

FIGURE 1A

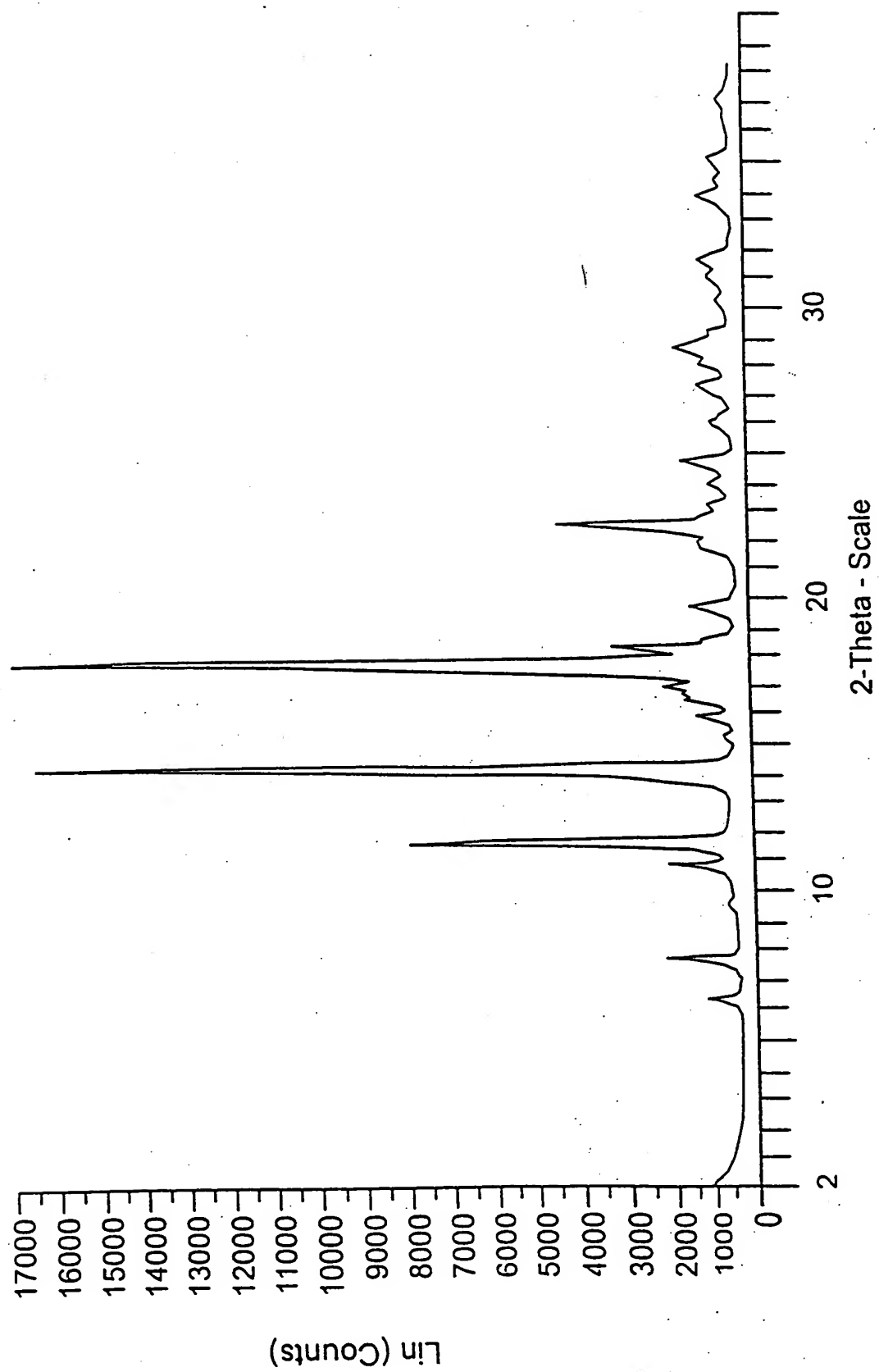


FIGURE 1B

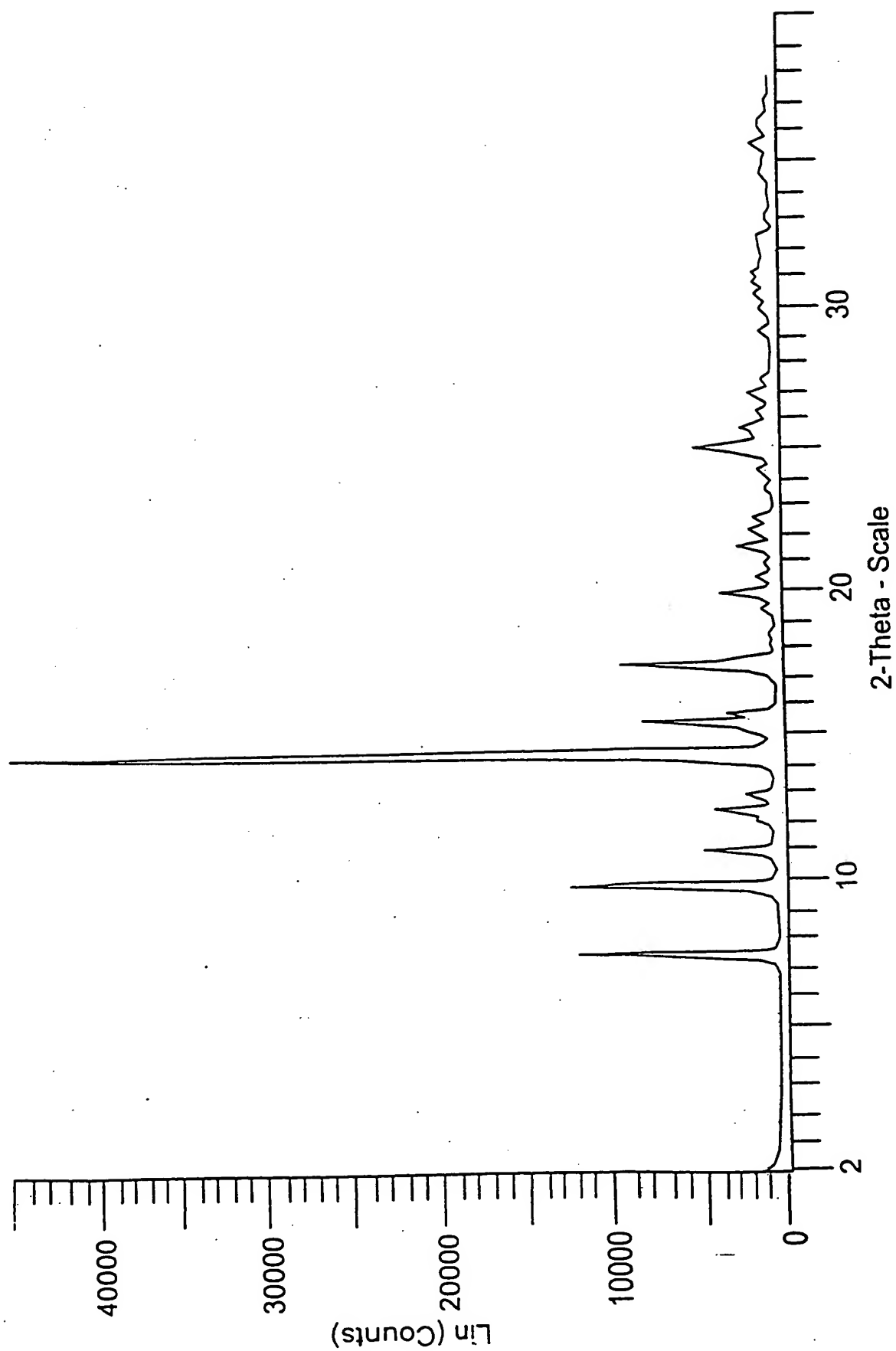


FIGURE 1C

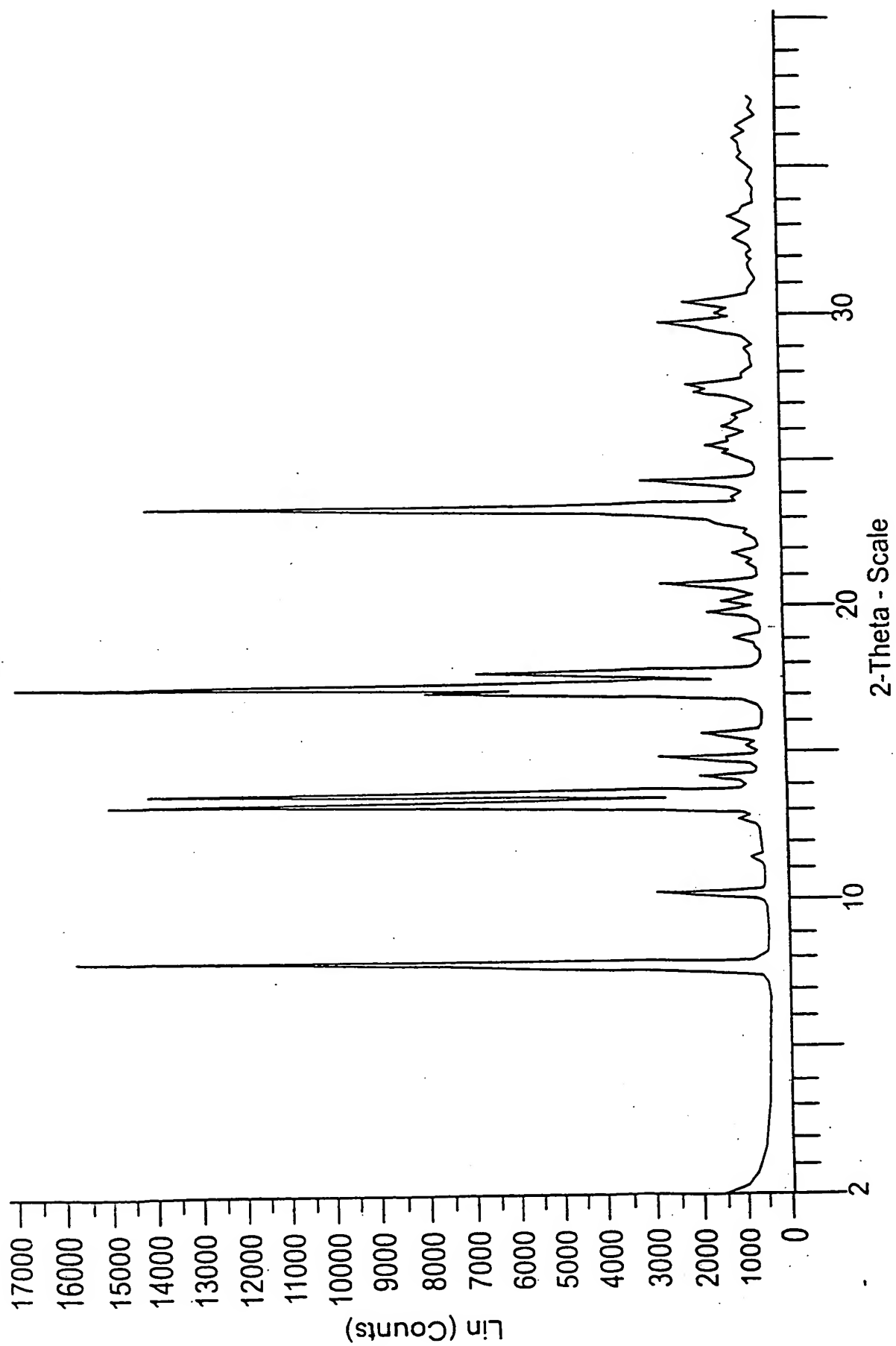


FIGURE 2A

Size: 0.6360 mg  
Method: 10 DEG C/MIN AMB TO 300  
Comment: SEALED PAN

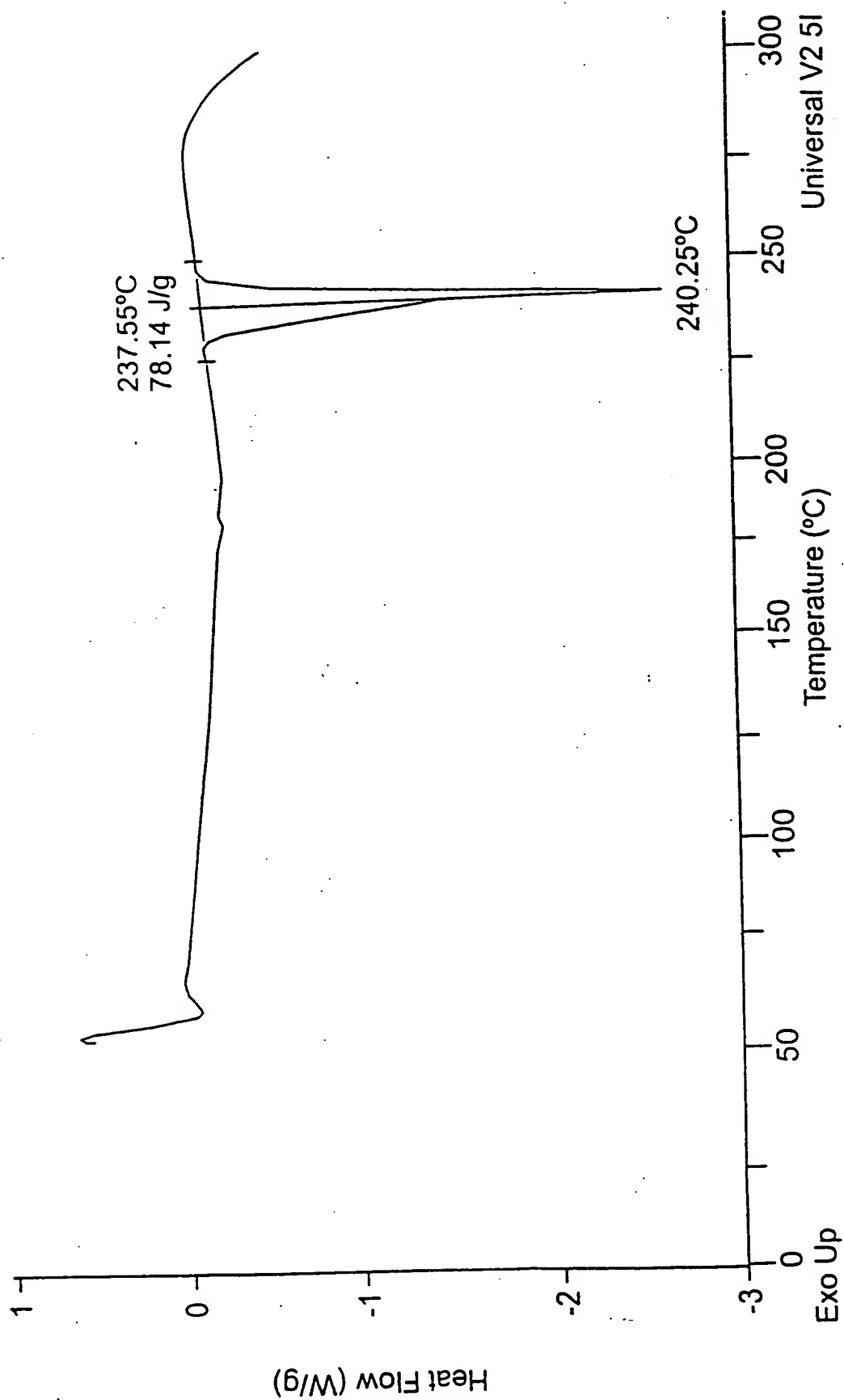
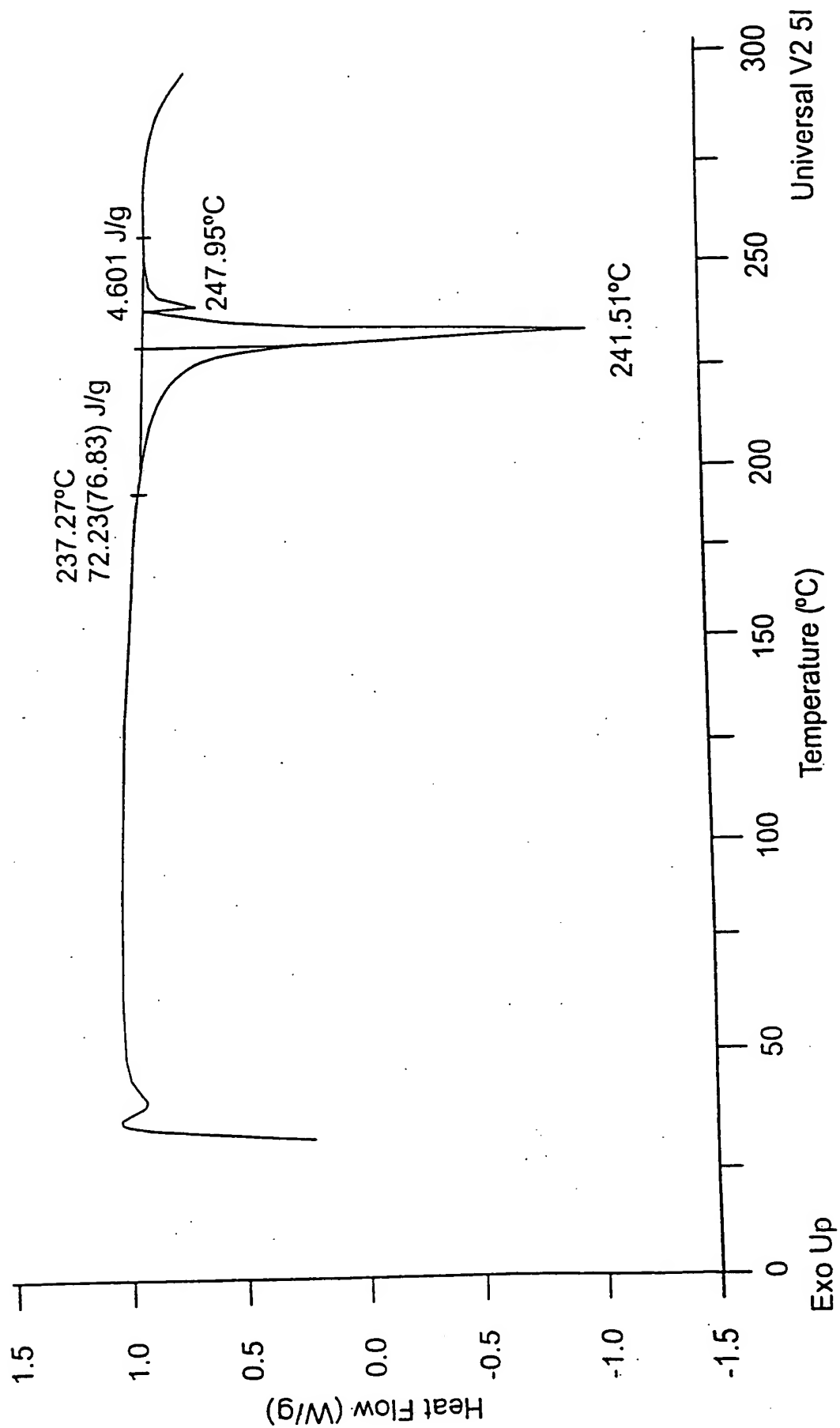


FIGURE 2B

Size: 1.7840 mg

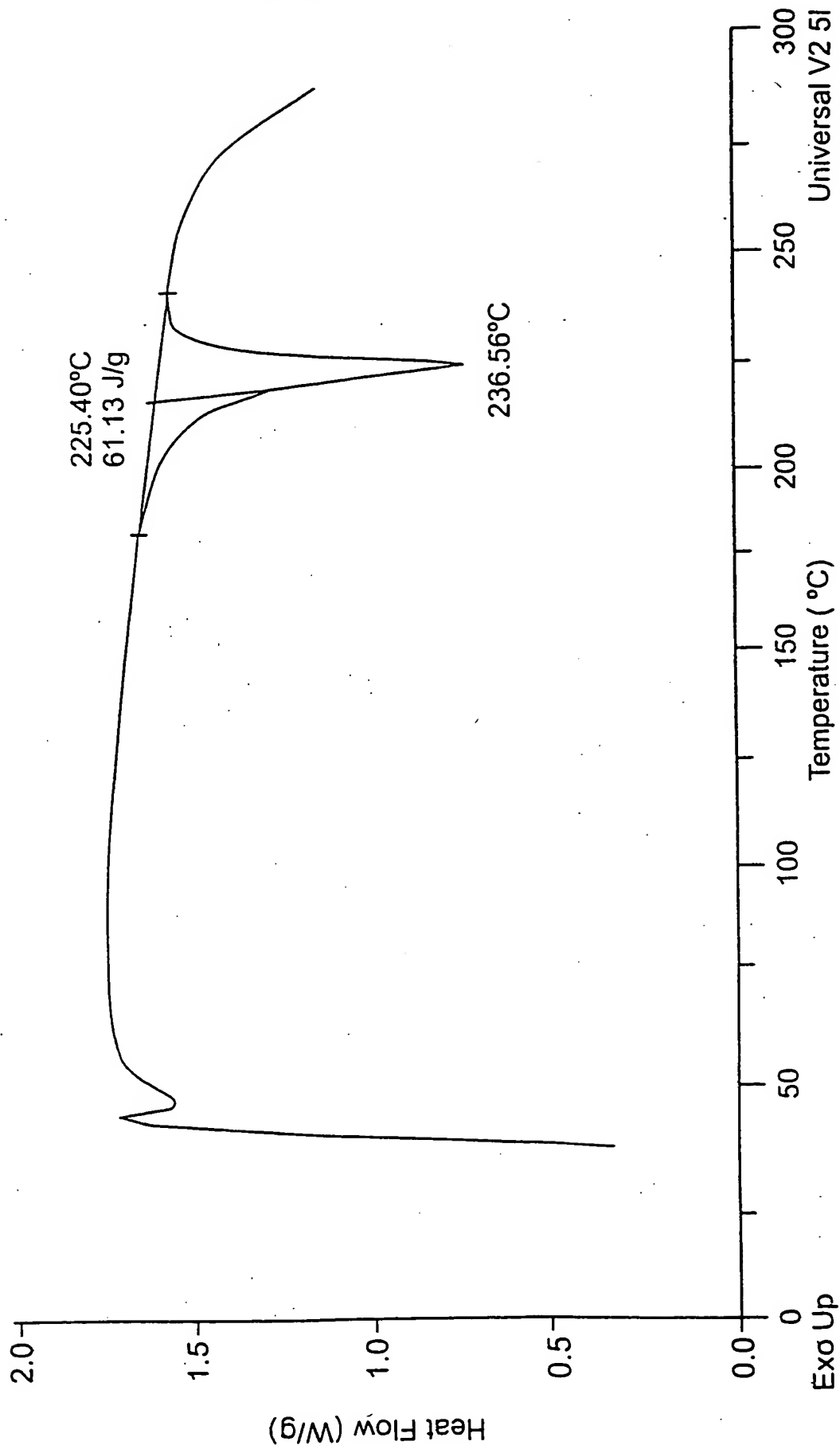
Method: 10 DEG C/MIN,AMB TO 300

Comment: SEALED PAN



Size: 1.4230 mg  
Method: 10 DEG C/MIN AMB TO 300  
Comment: SEALED PAN

FIGURE 2C



# FIGURE 2D

Size: 1.0400 mg  
Method: 10 DEG C/MIN AMB TO 300  
Comment: SEALED PAN

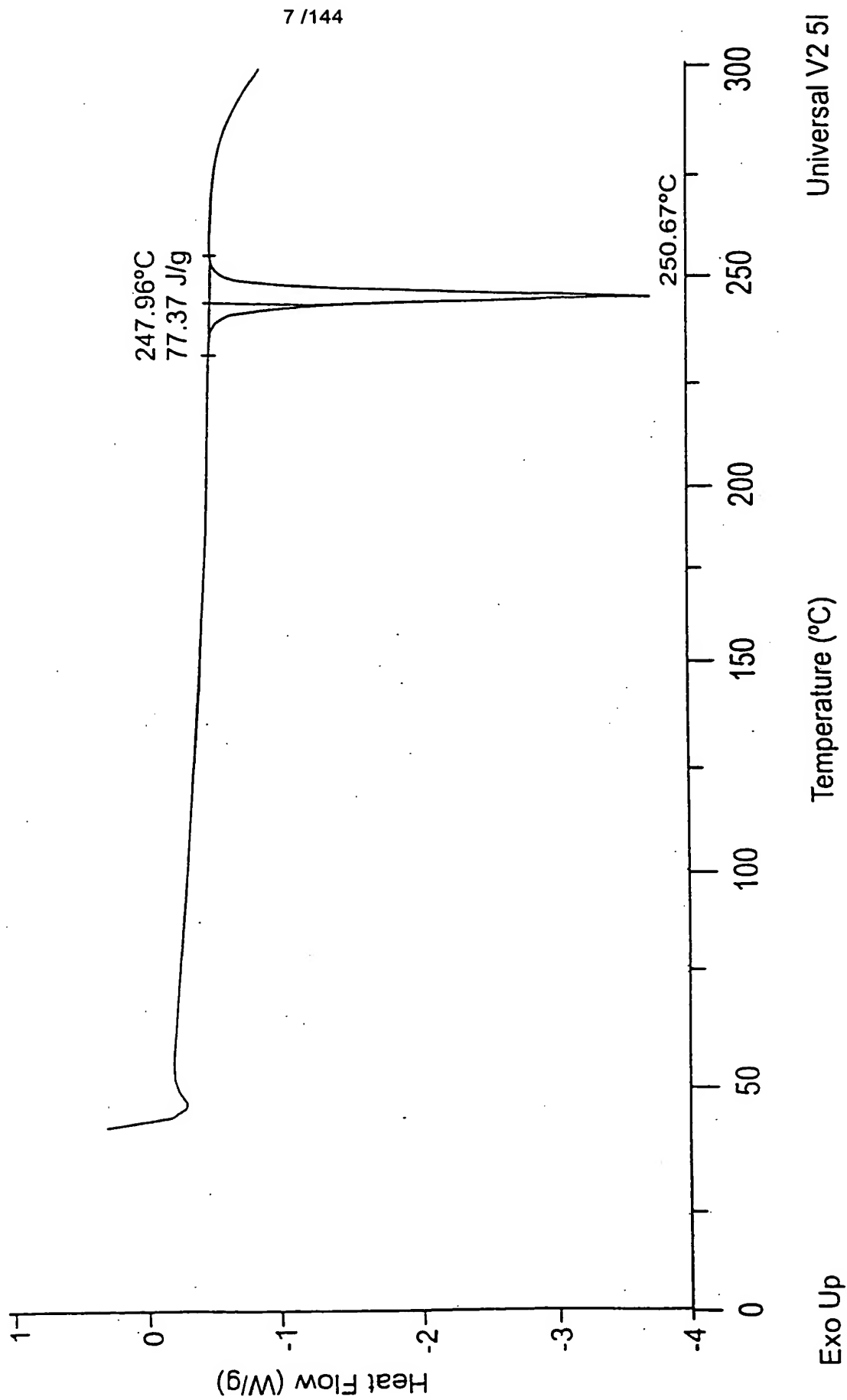


FIGURE 3A

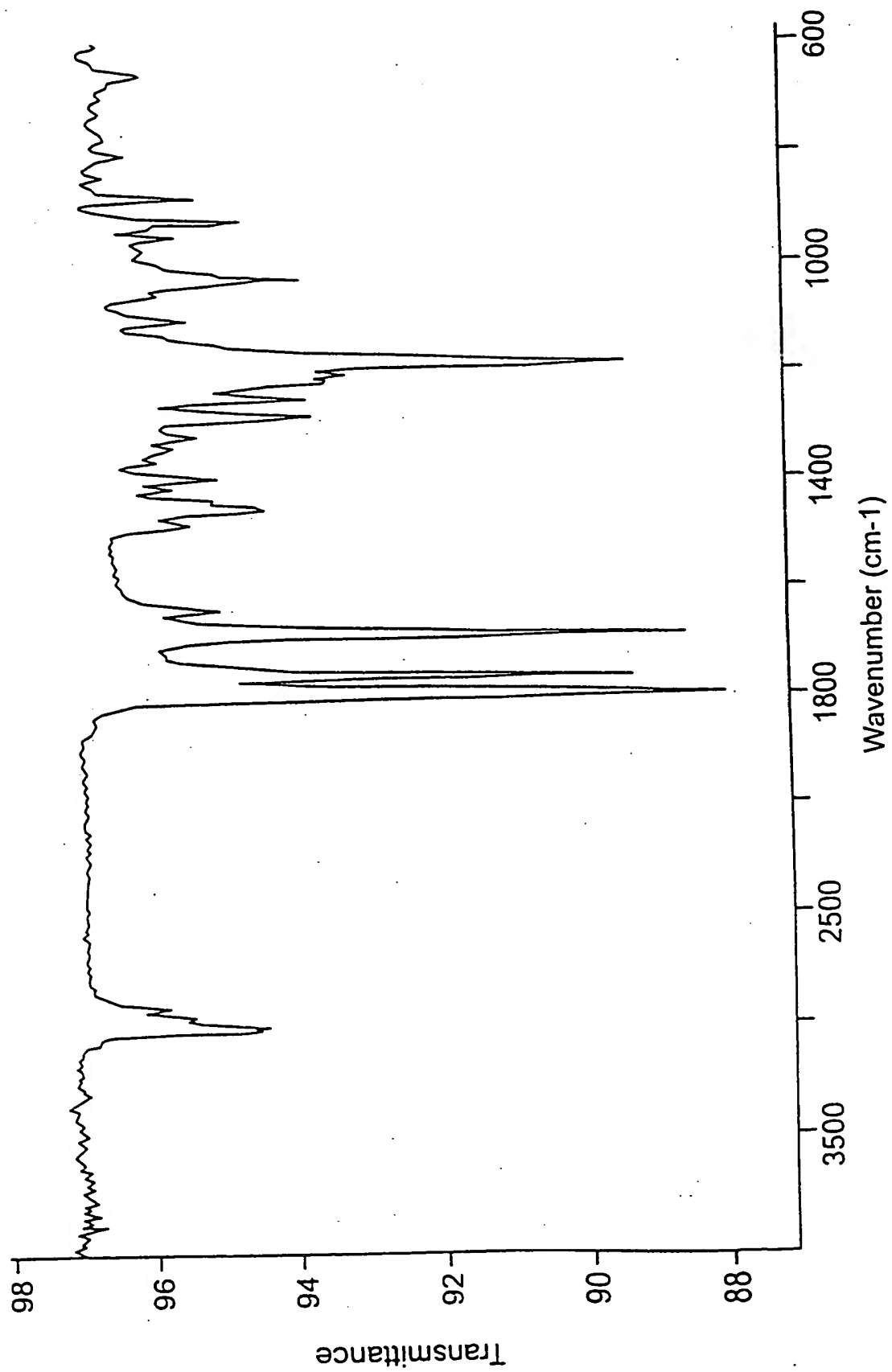




FIGURE 3B

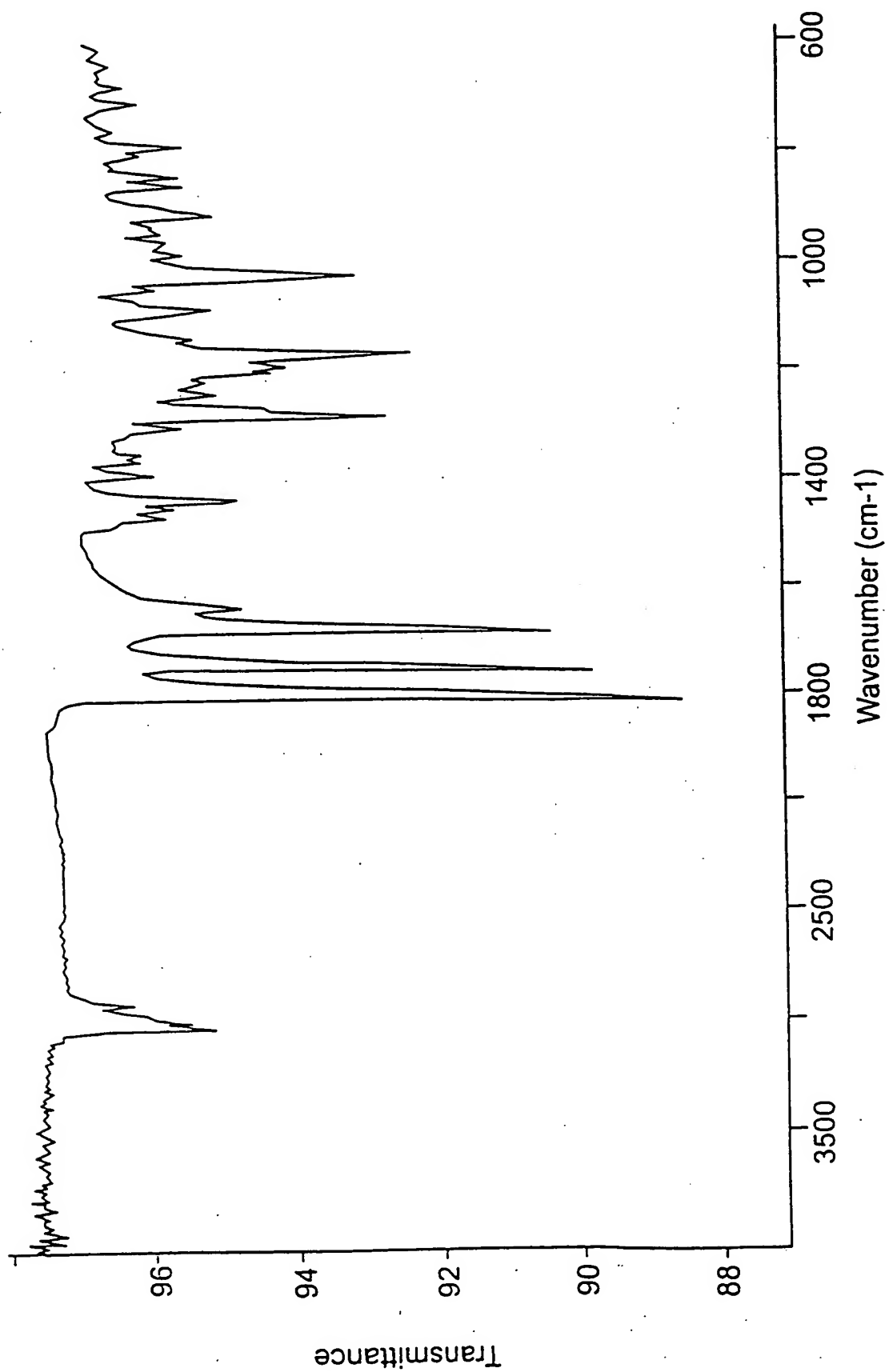
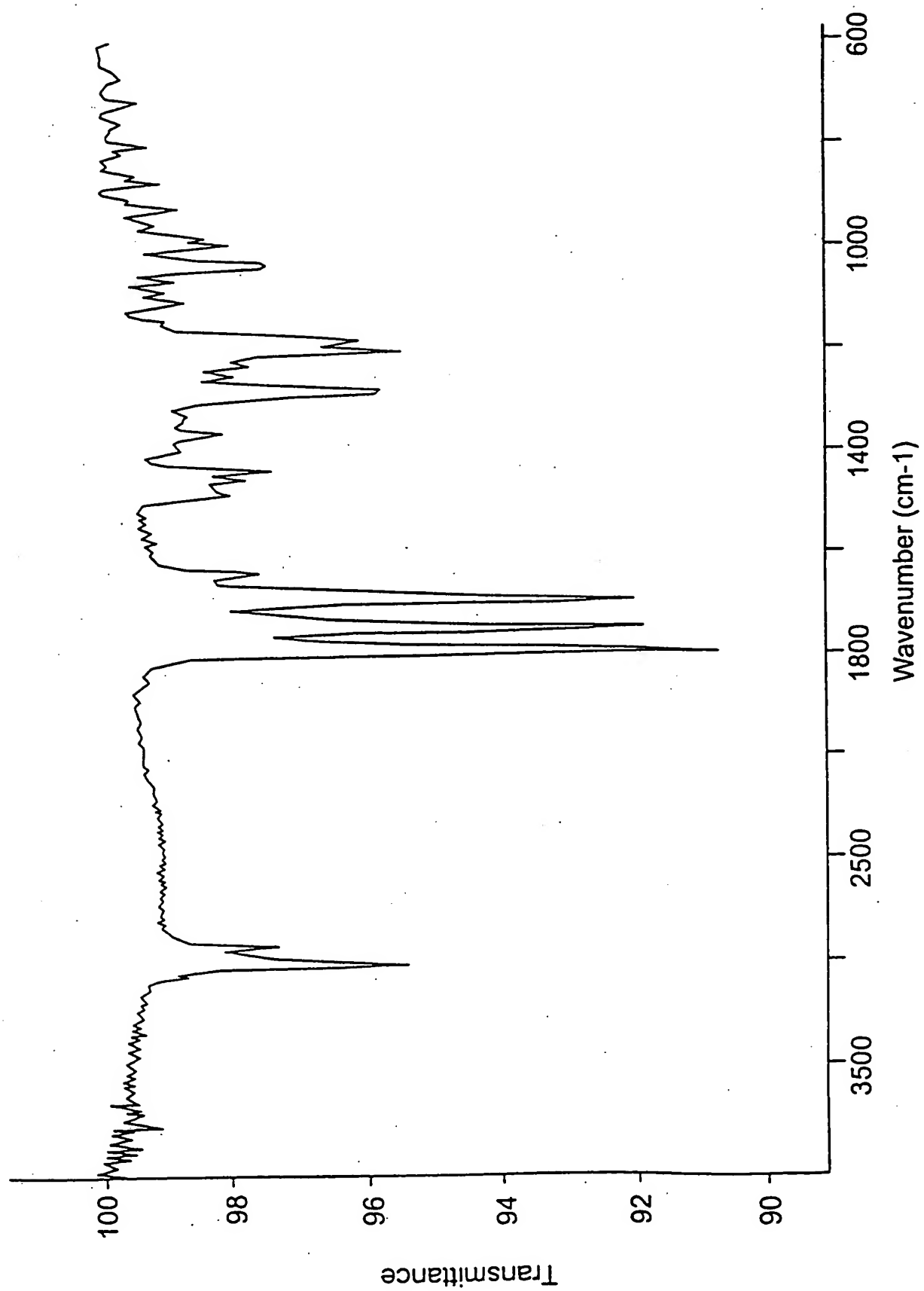


FIGURE 3C



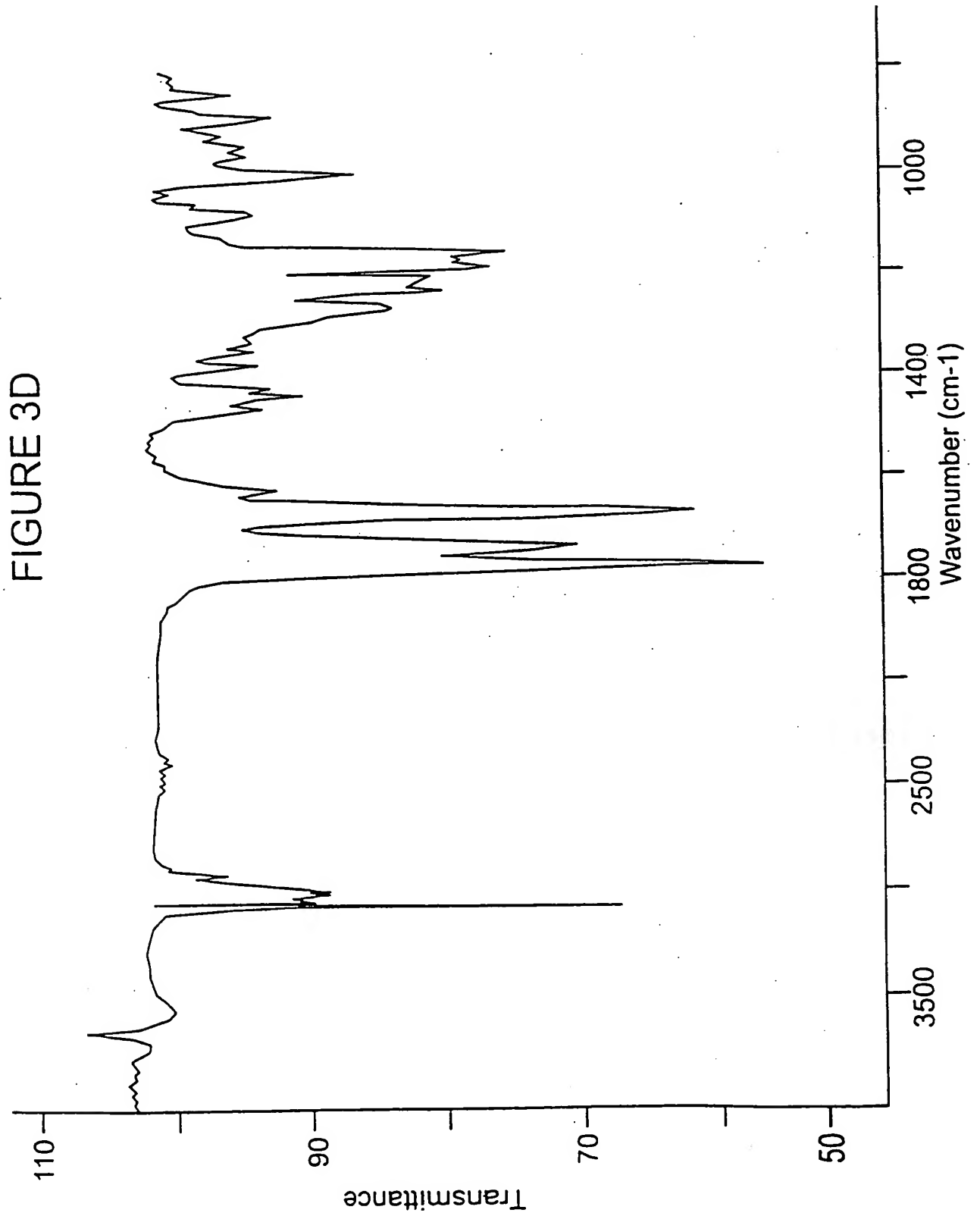


FIGURE 4

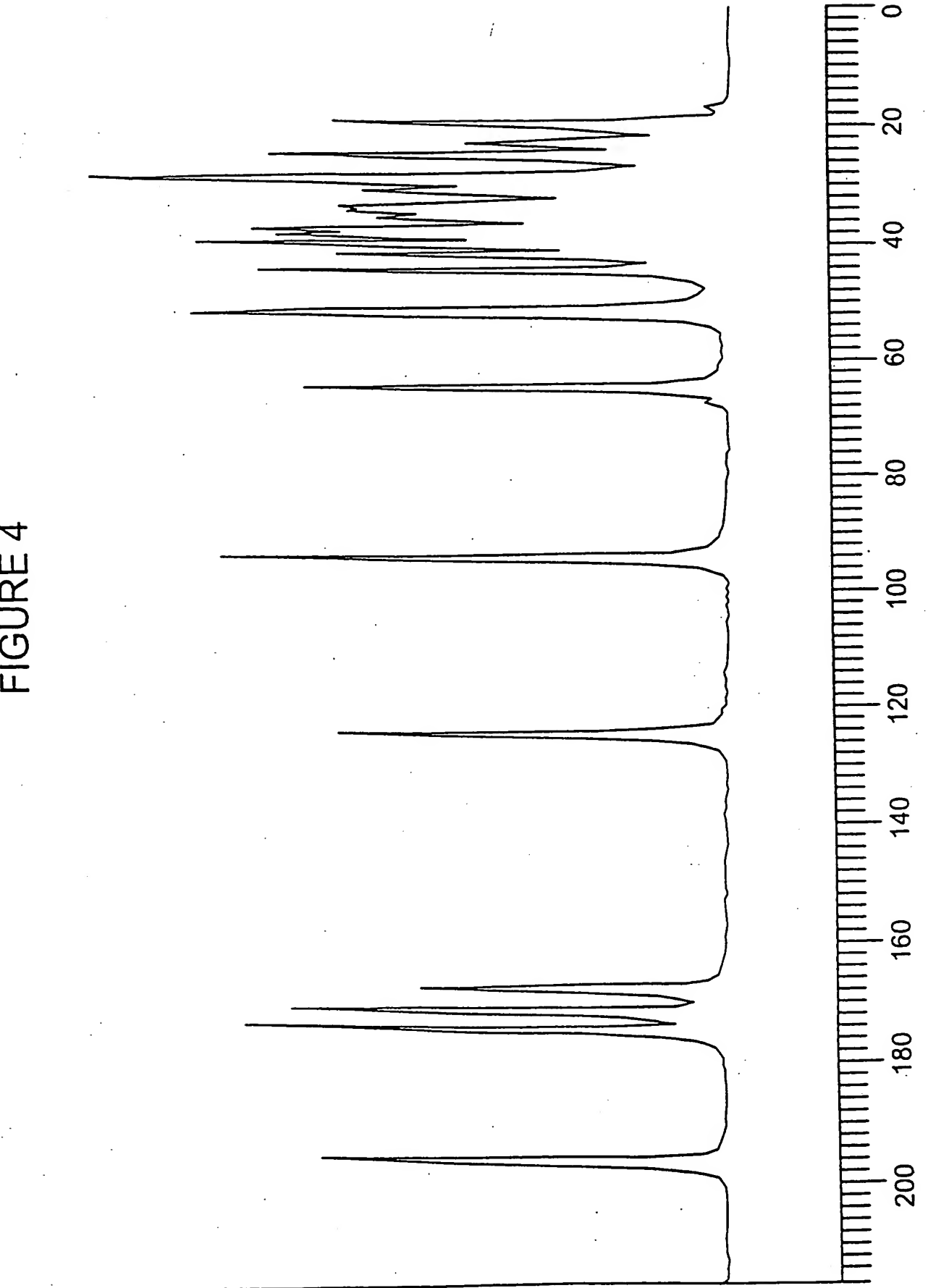


FIGURE 5

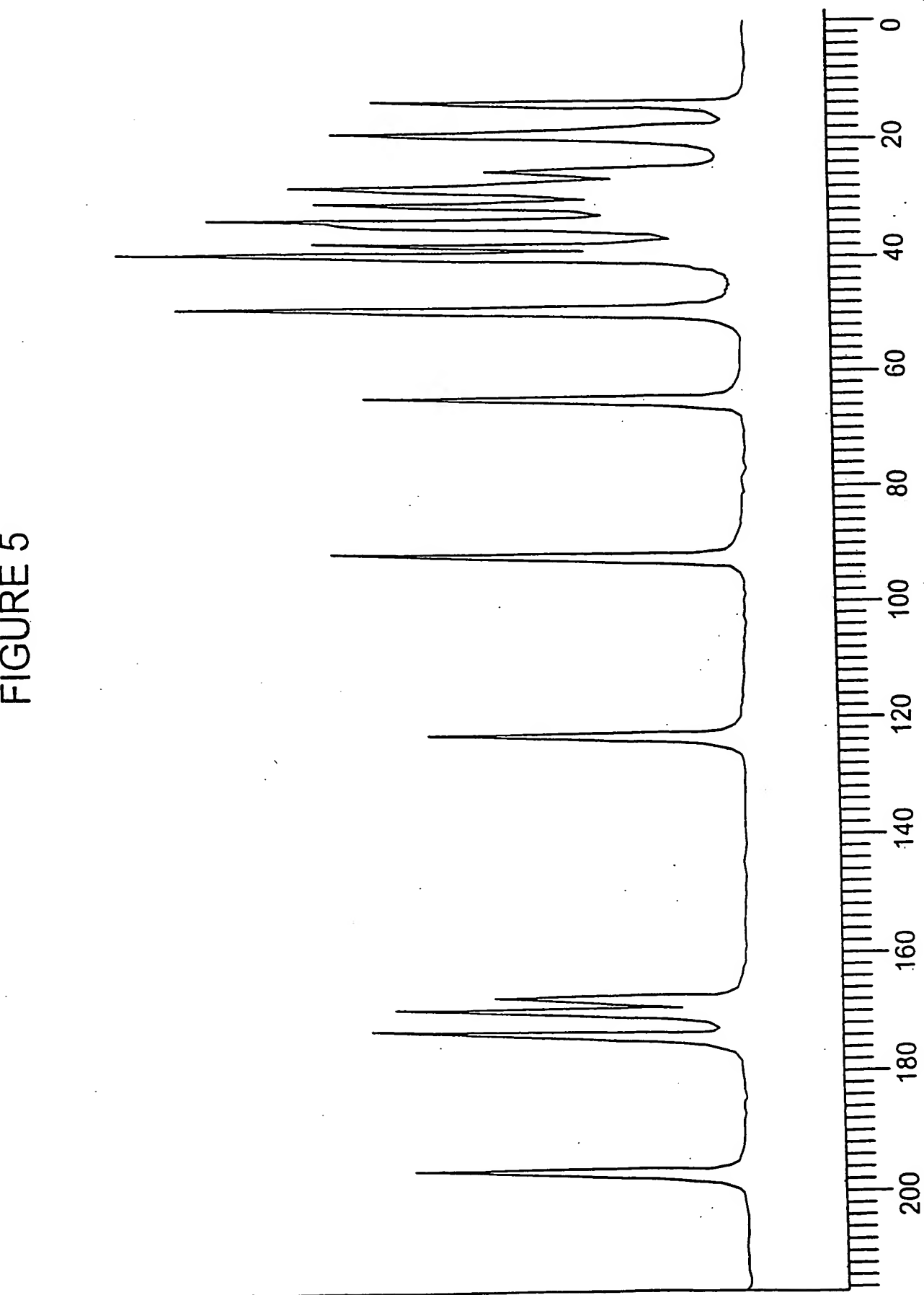


FIGURE 6A

methyl ethyl ketone solvent

Size: 3.3010 mg

Method: 10 deg ramp to 300 deg

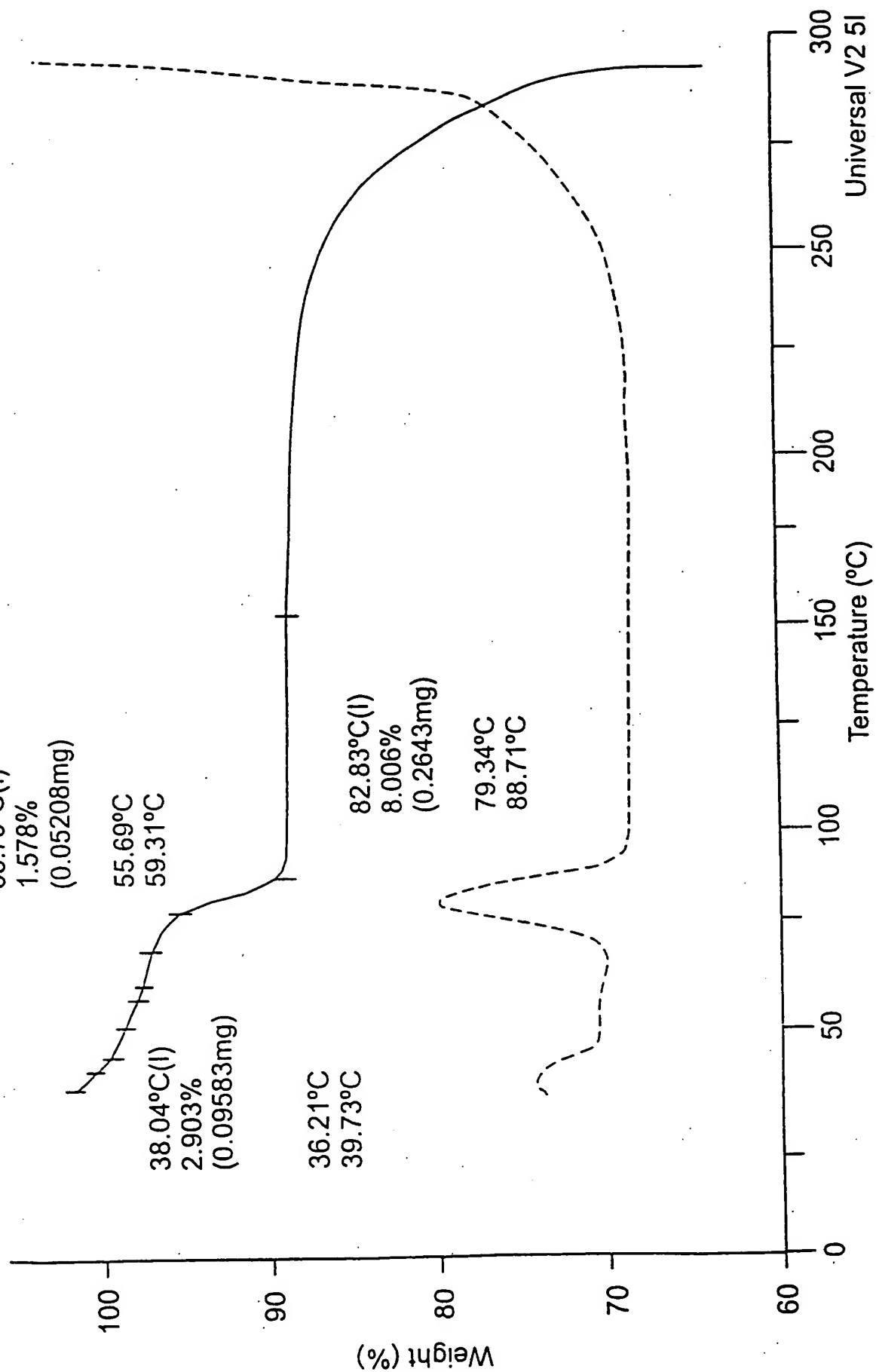


FIGURE 7

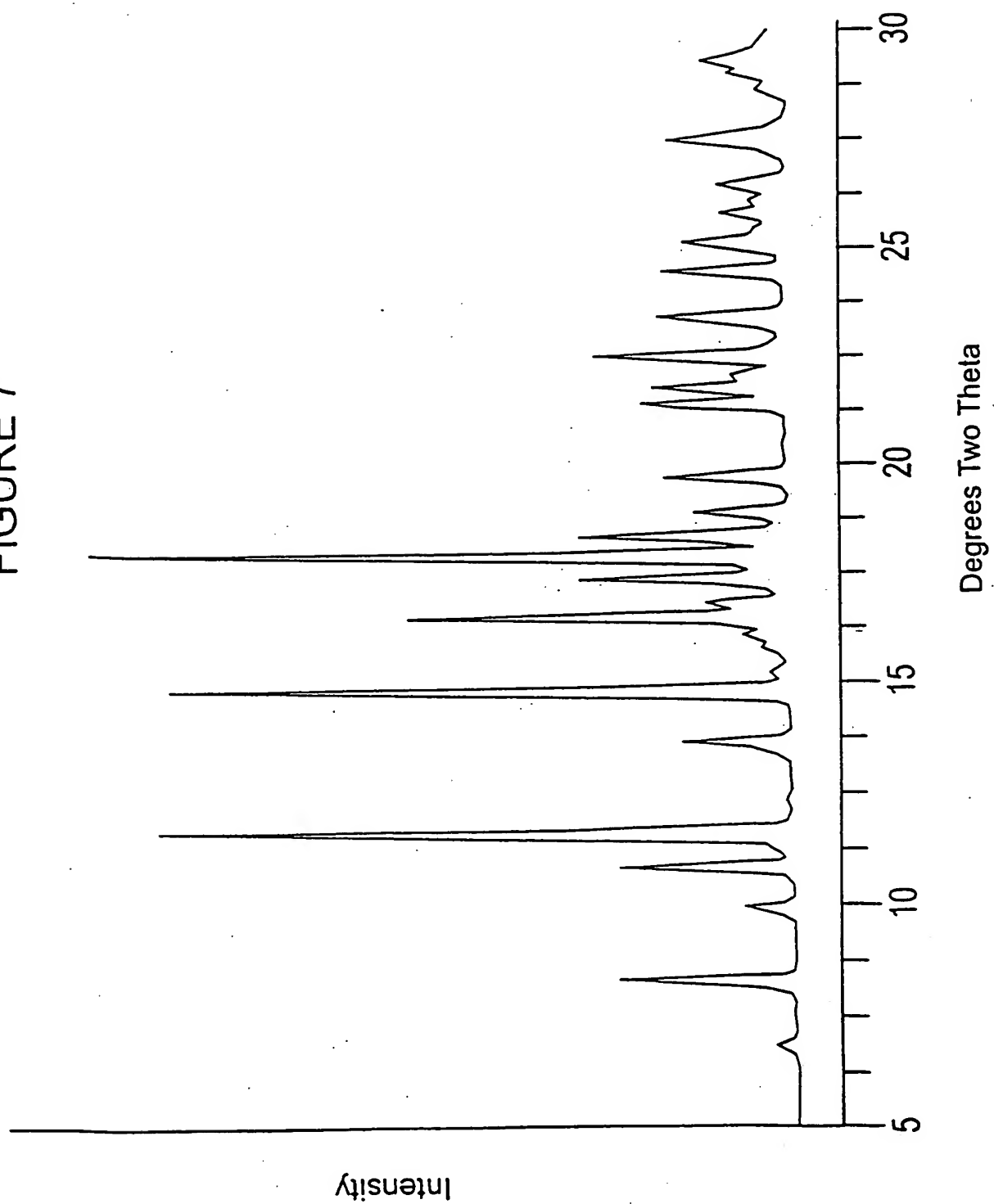


FIGURE 8

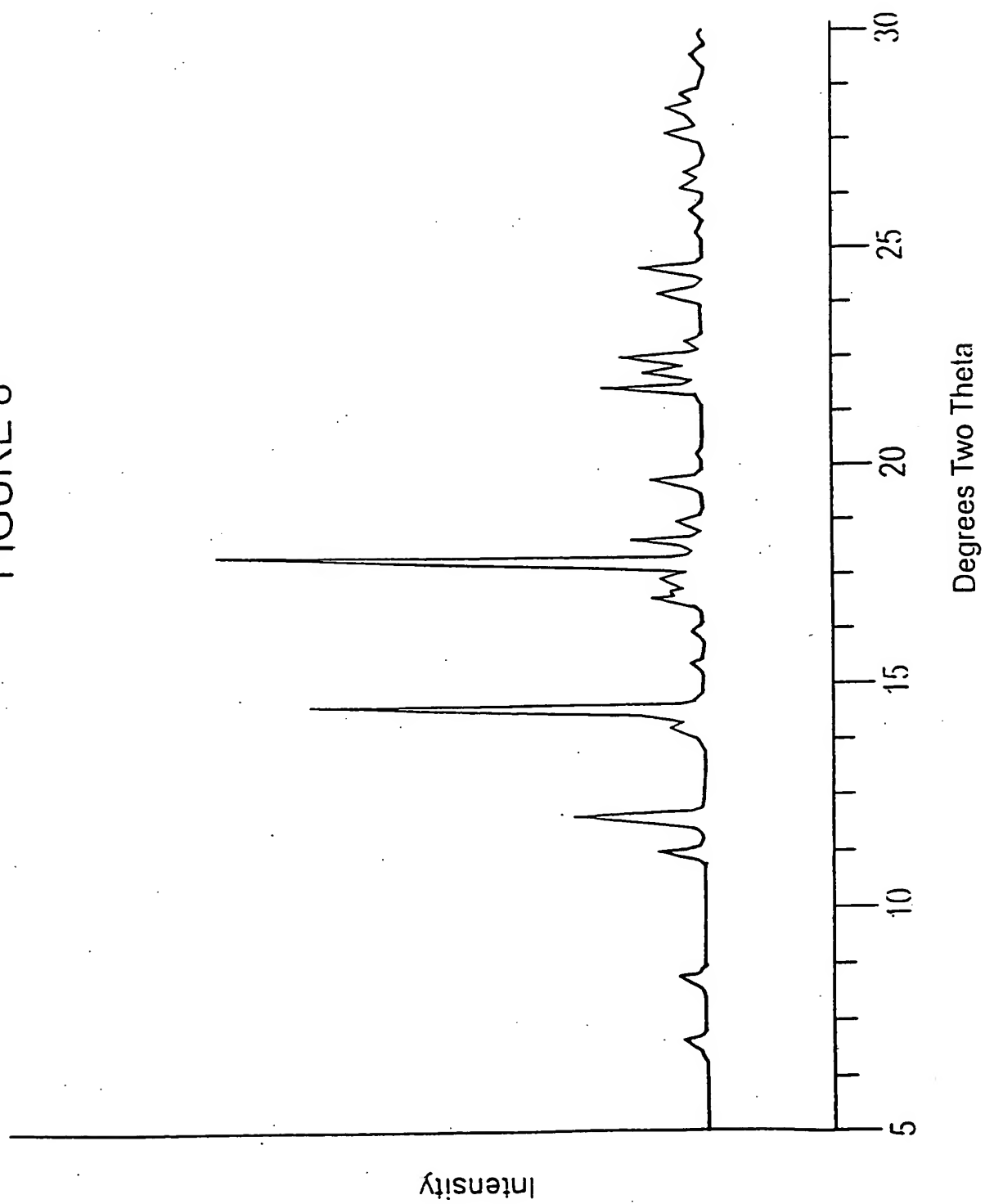
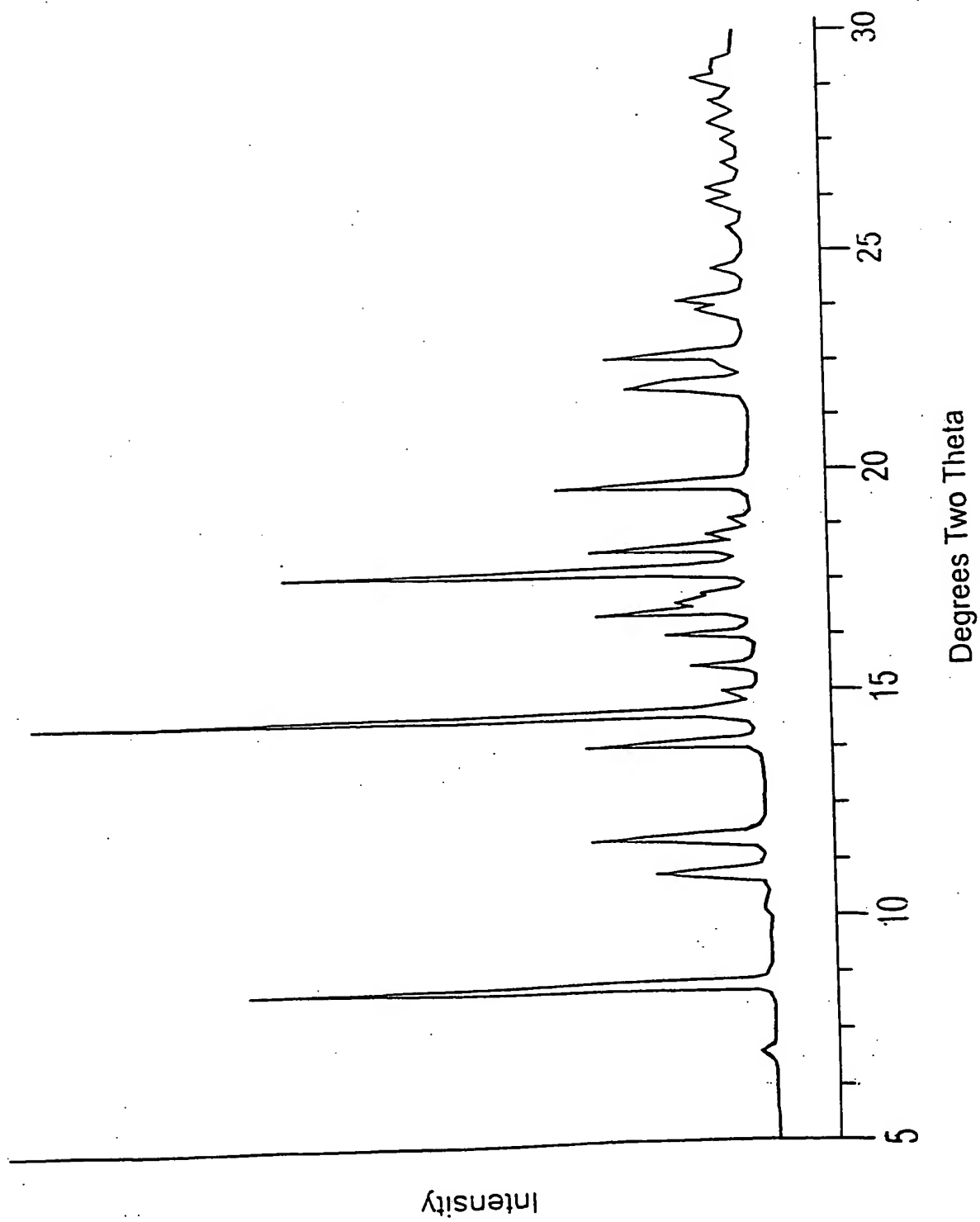




FIGURE 9



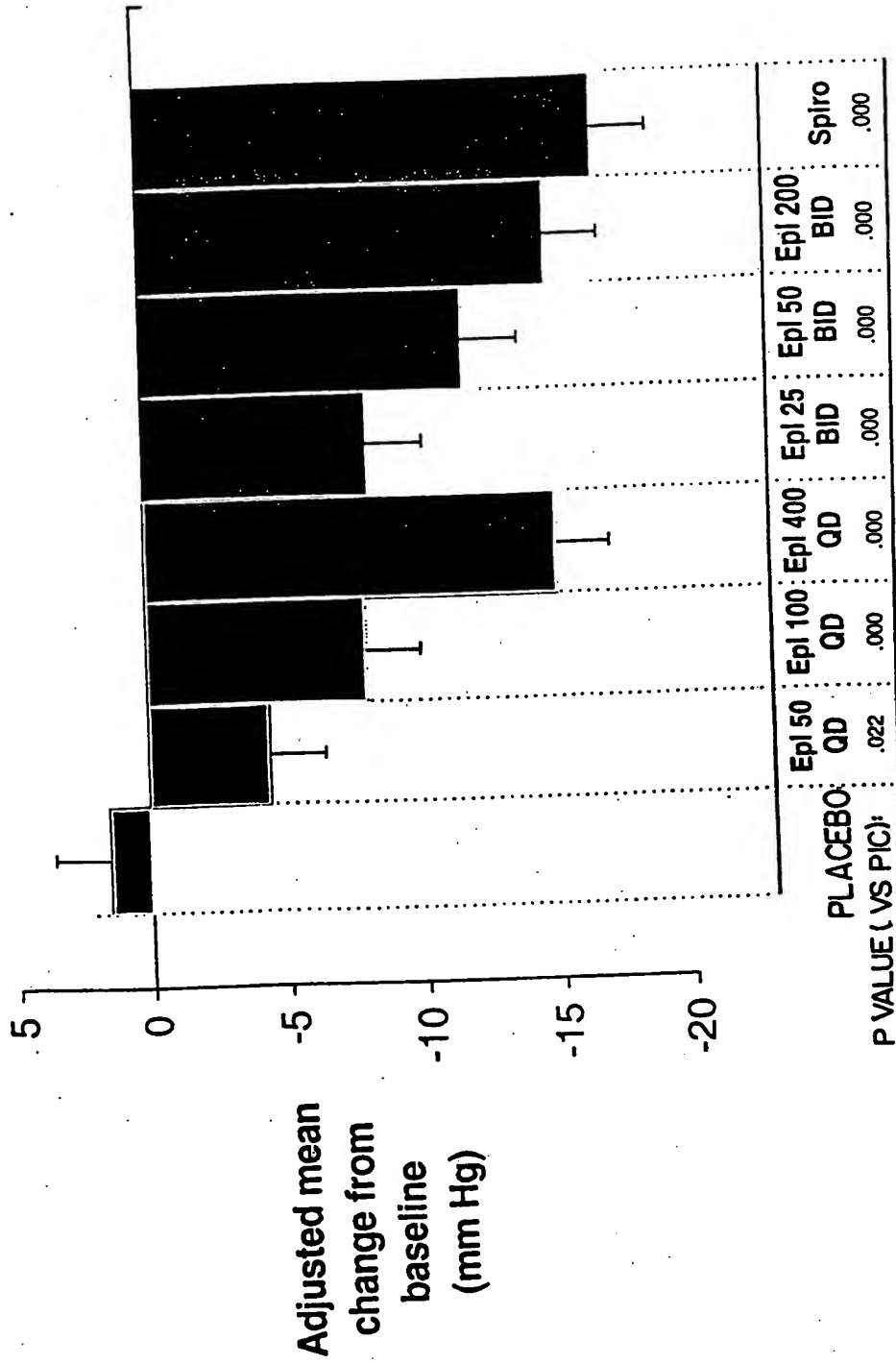


Figure 10

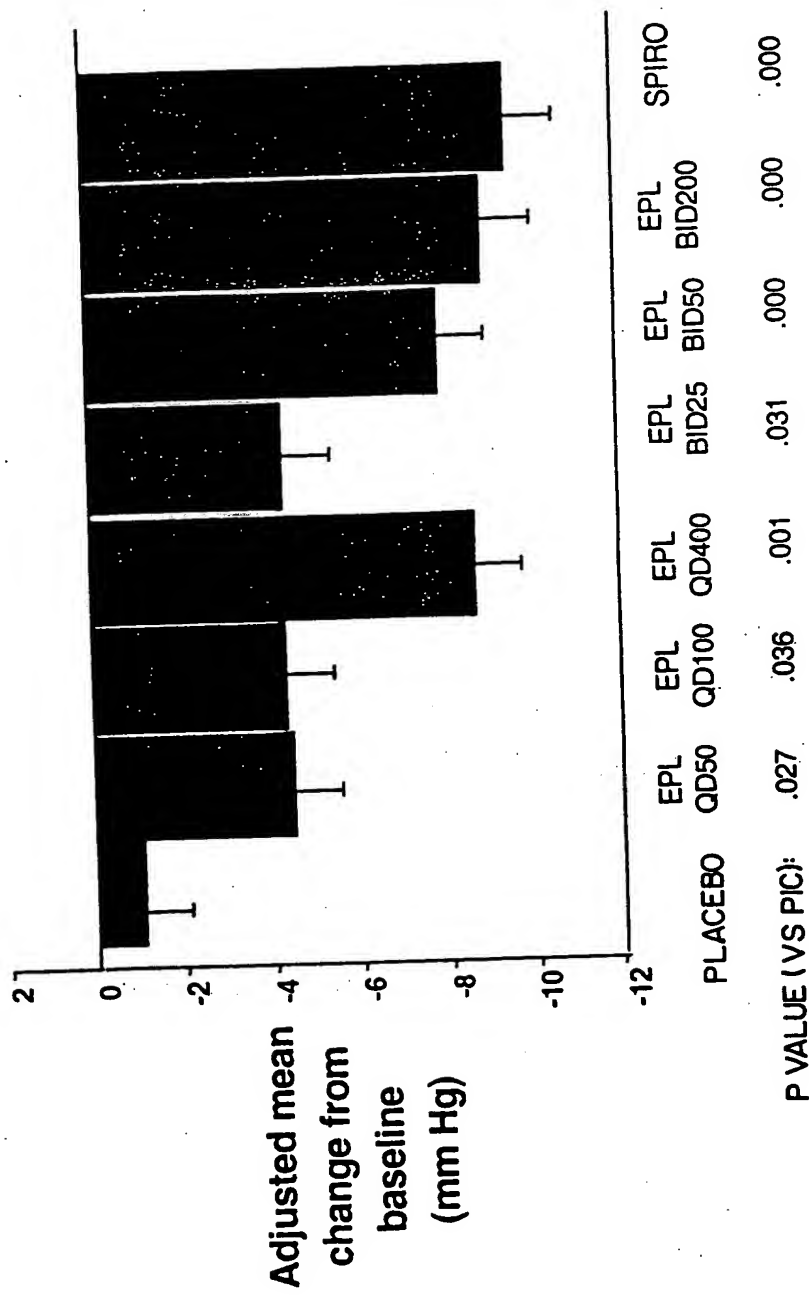


Figure 11

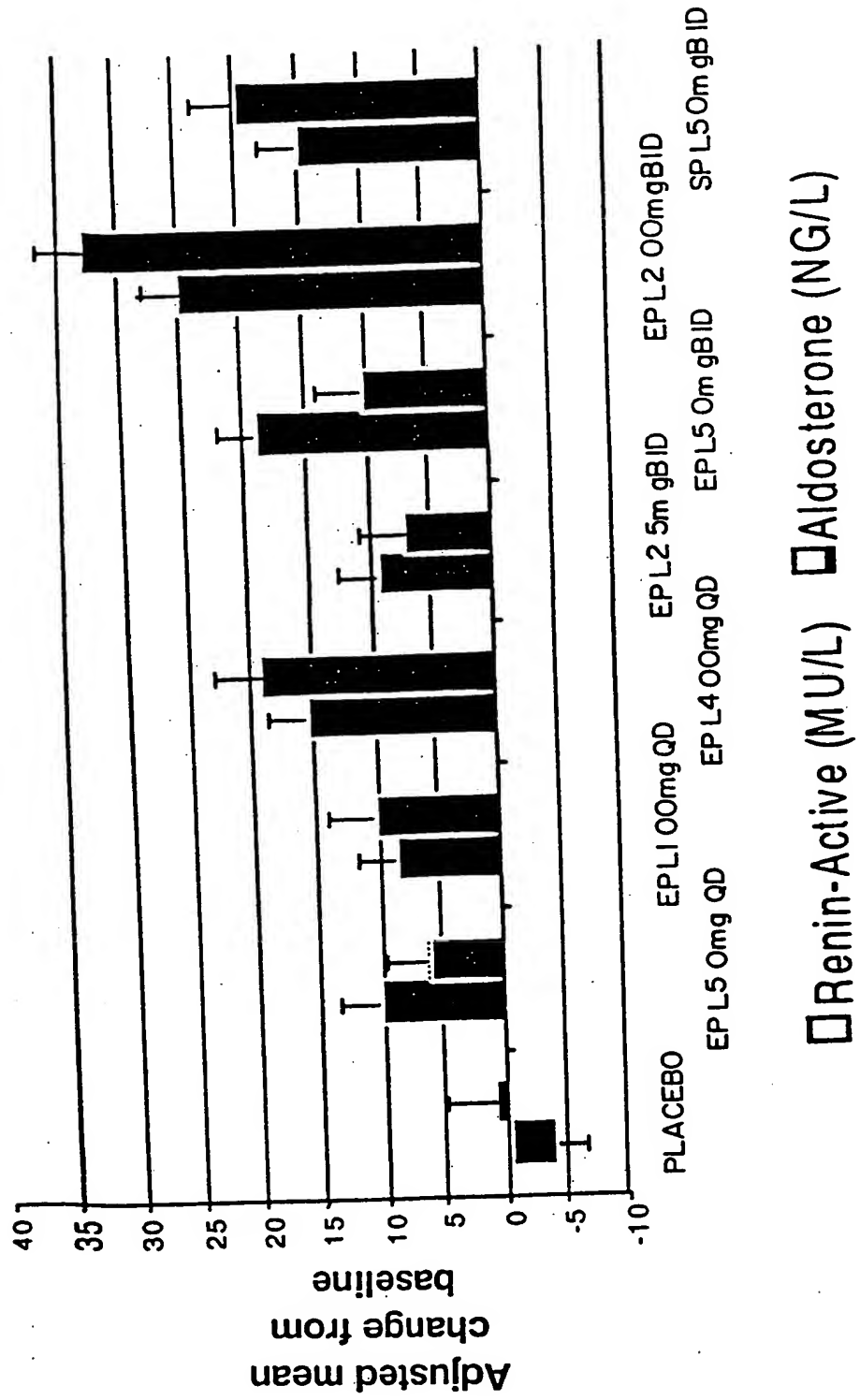
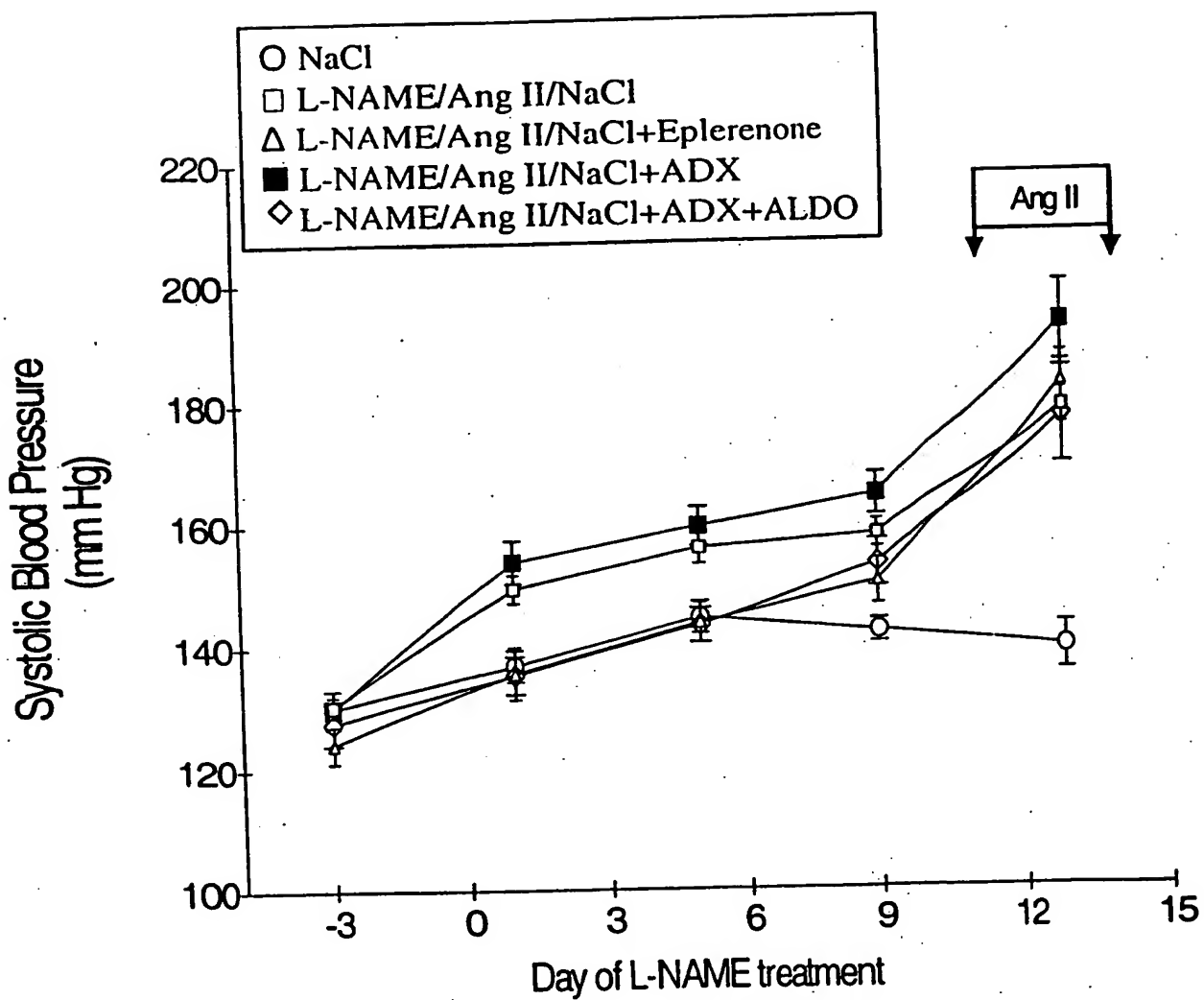
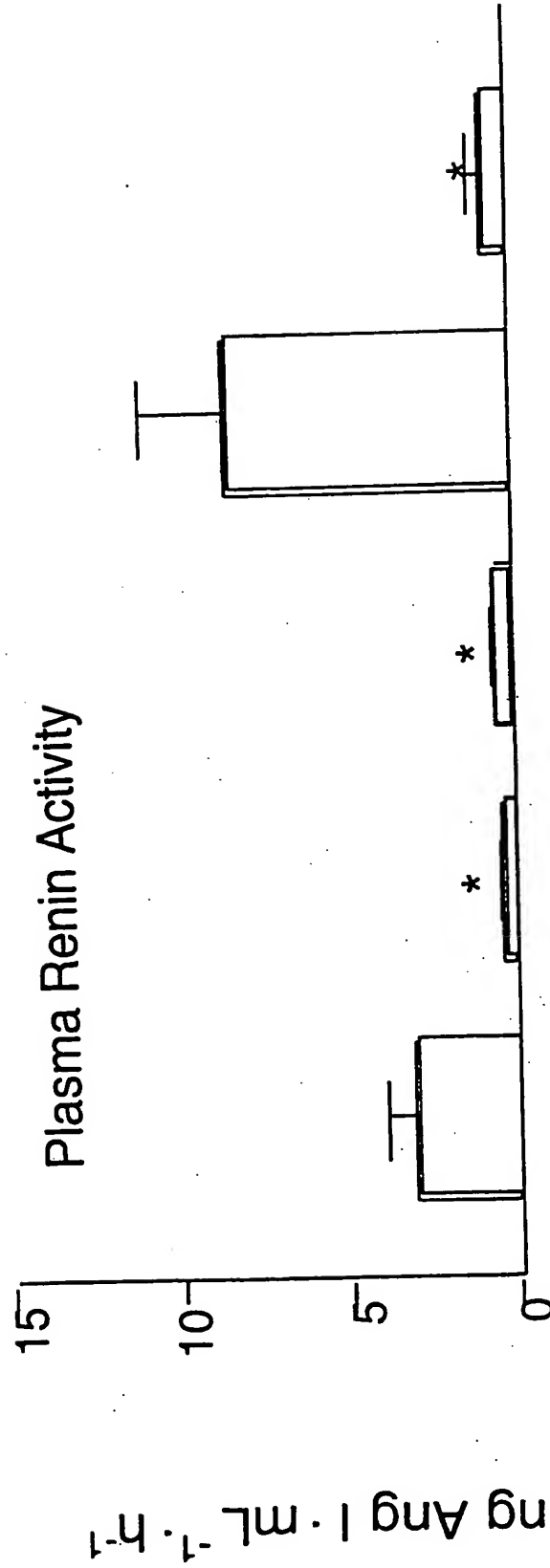


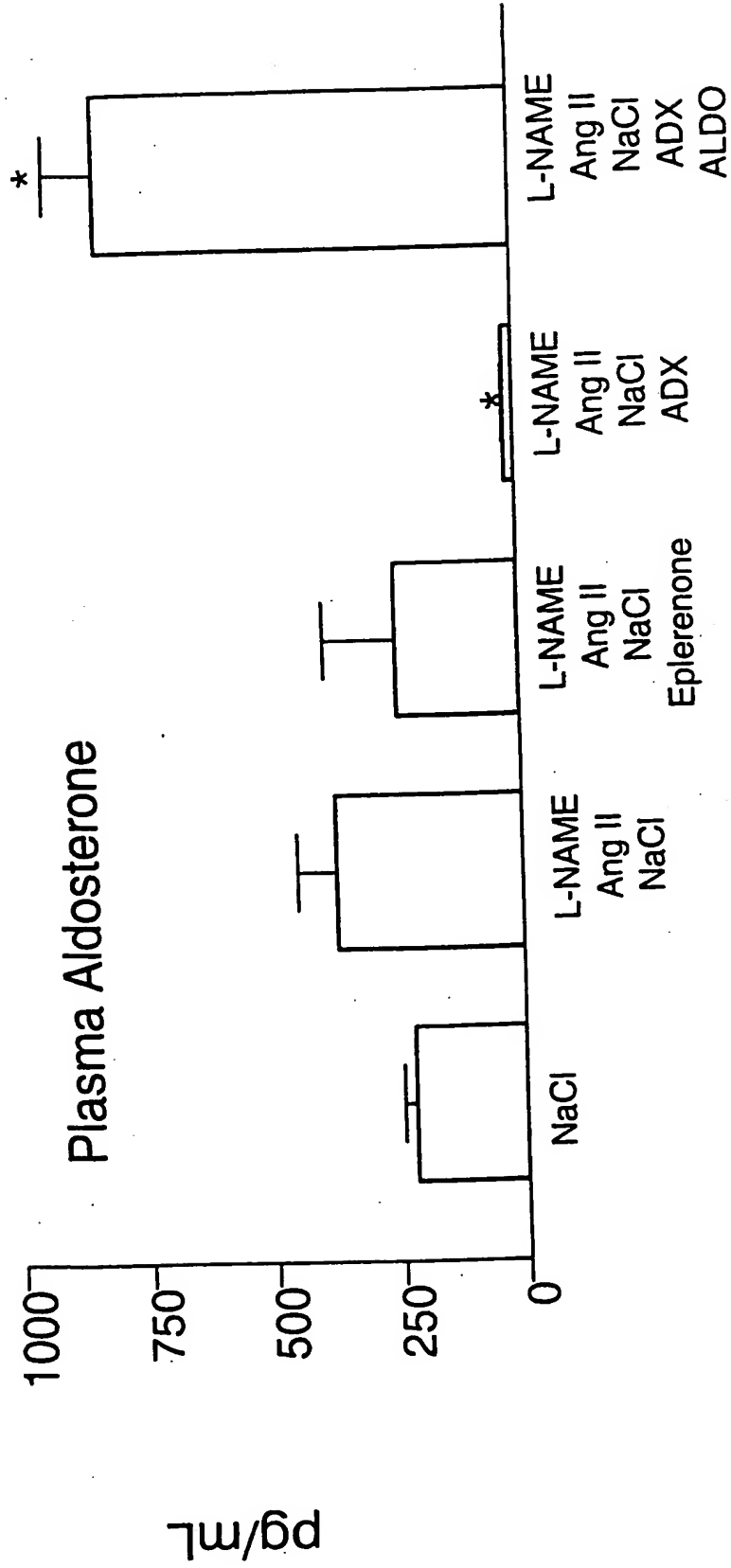
Figure 12



**Figure A-1. Systolic blood pressure.**



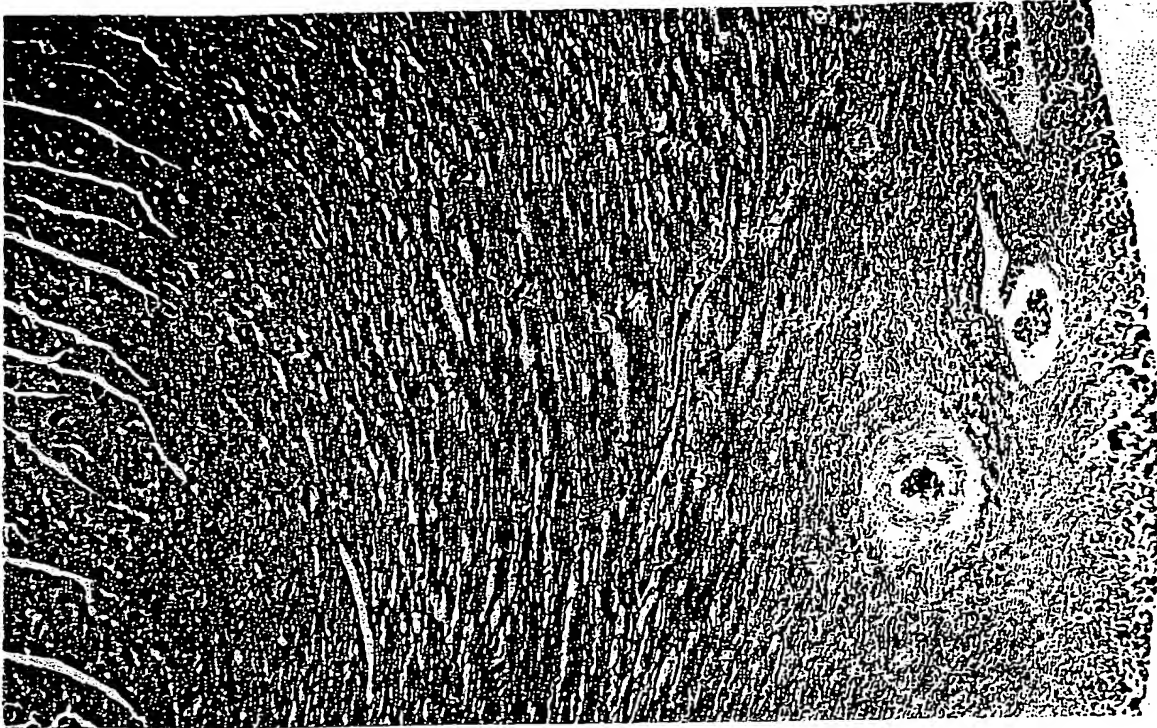
**Figure A-2 (A) Plasma renin activity determined after sacrifice.**



**Figure A-2 (B) Plasma aldosterone levels determined after sacrifice.**

FIGURE A-3

A



B

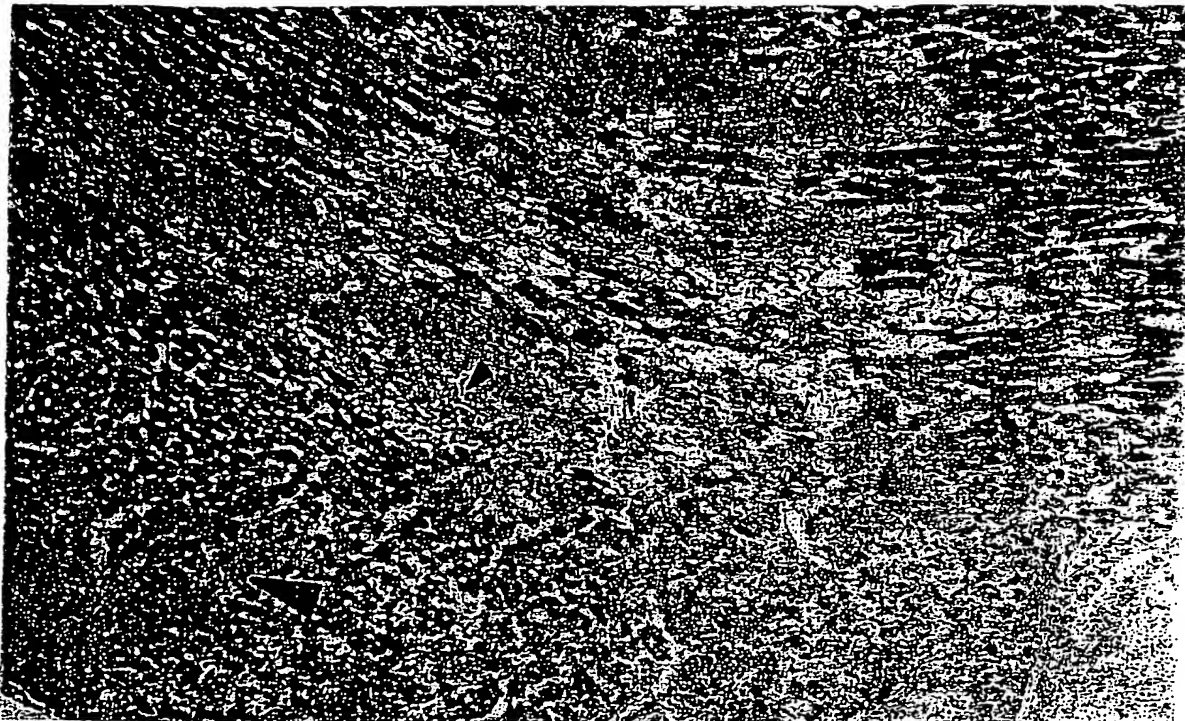
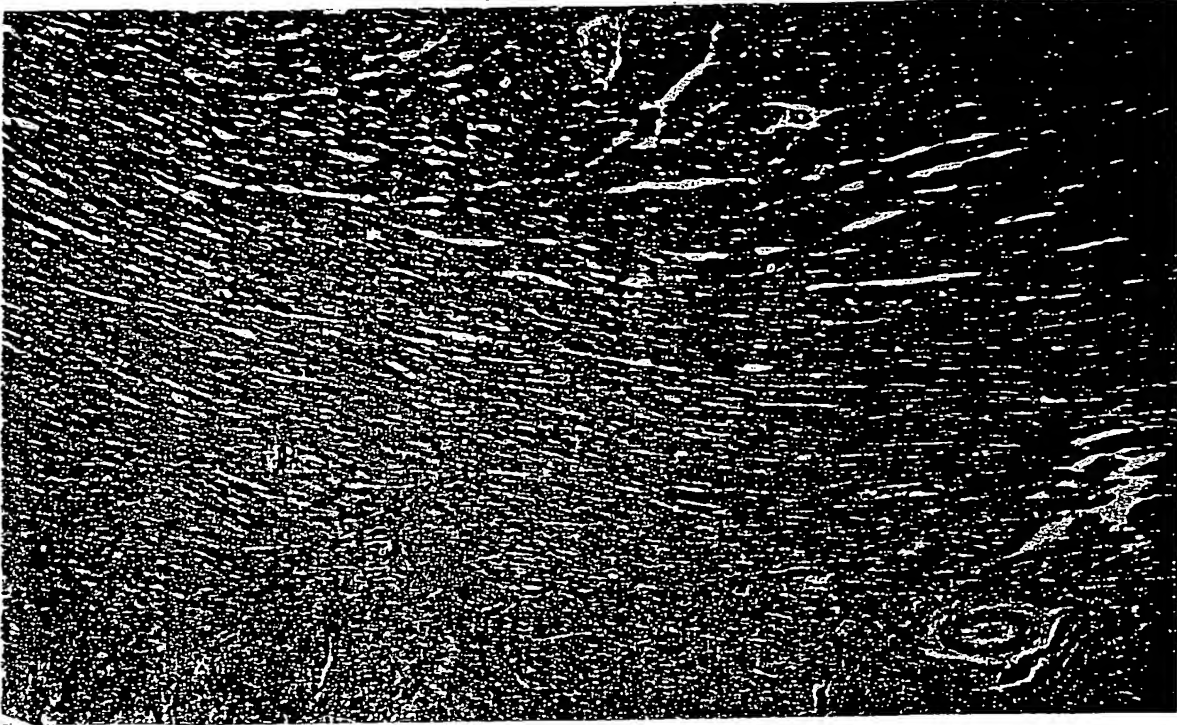


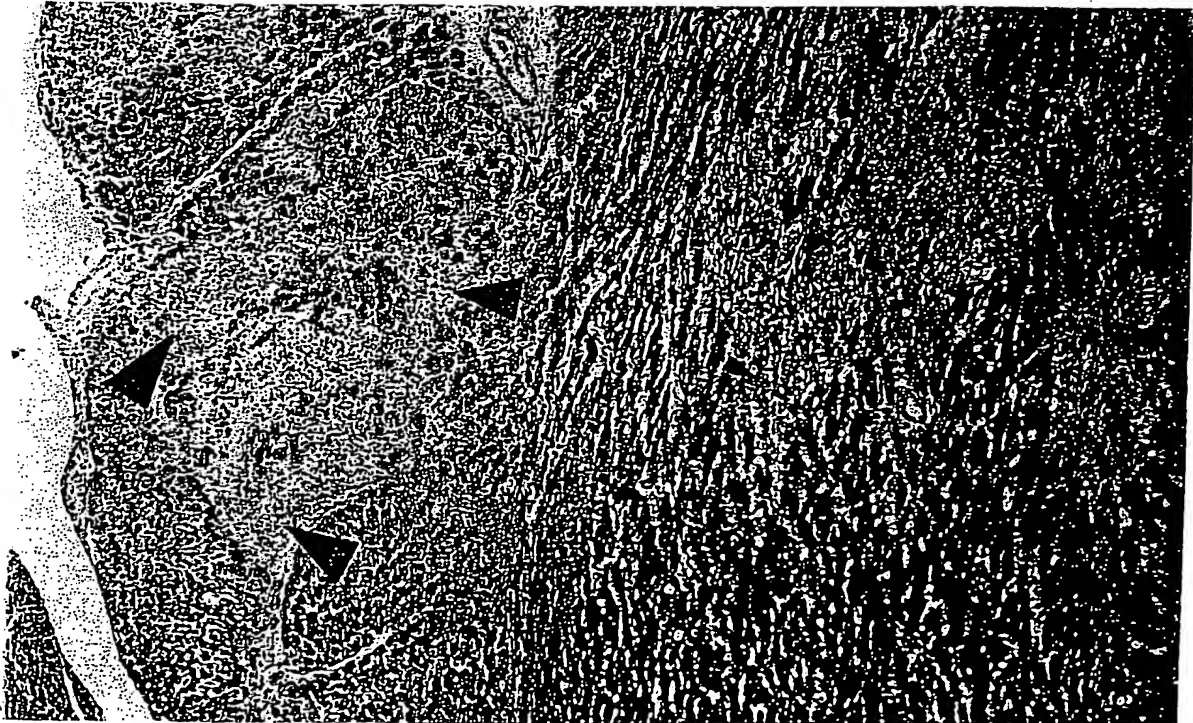


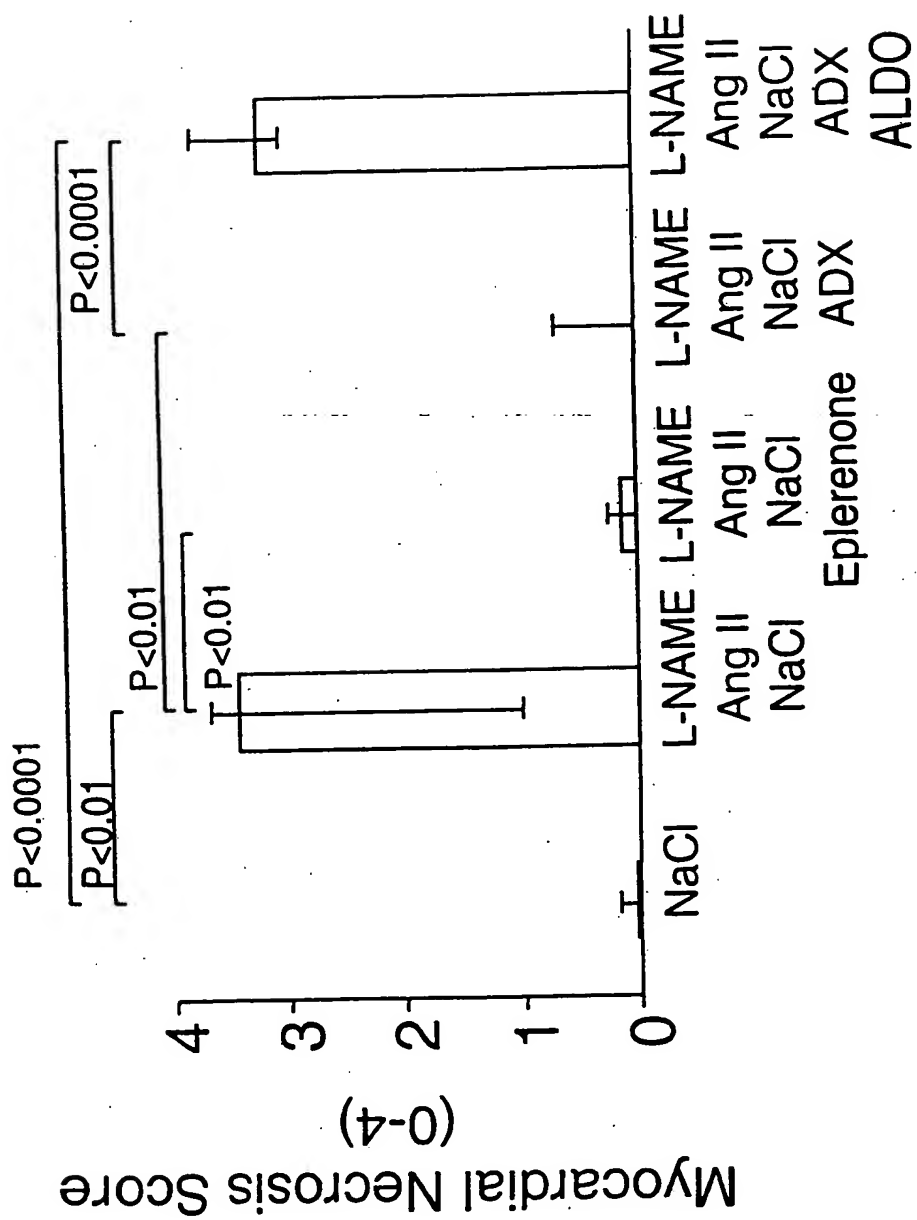
FIGURE A-3

C

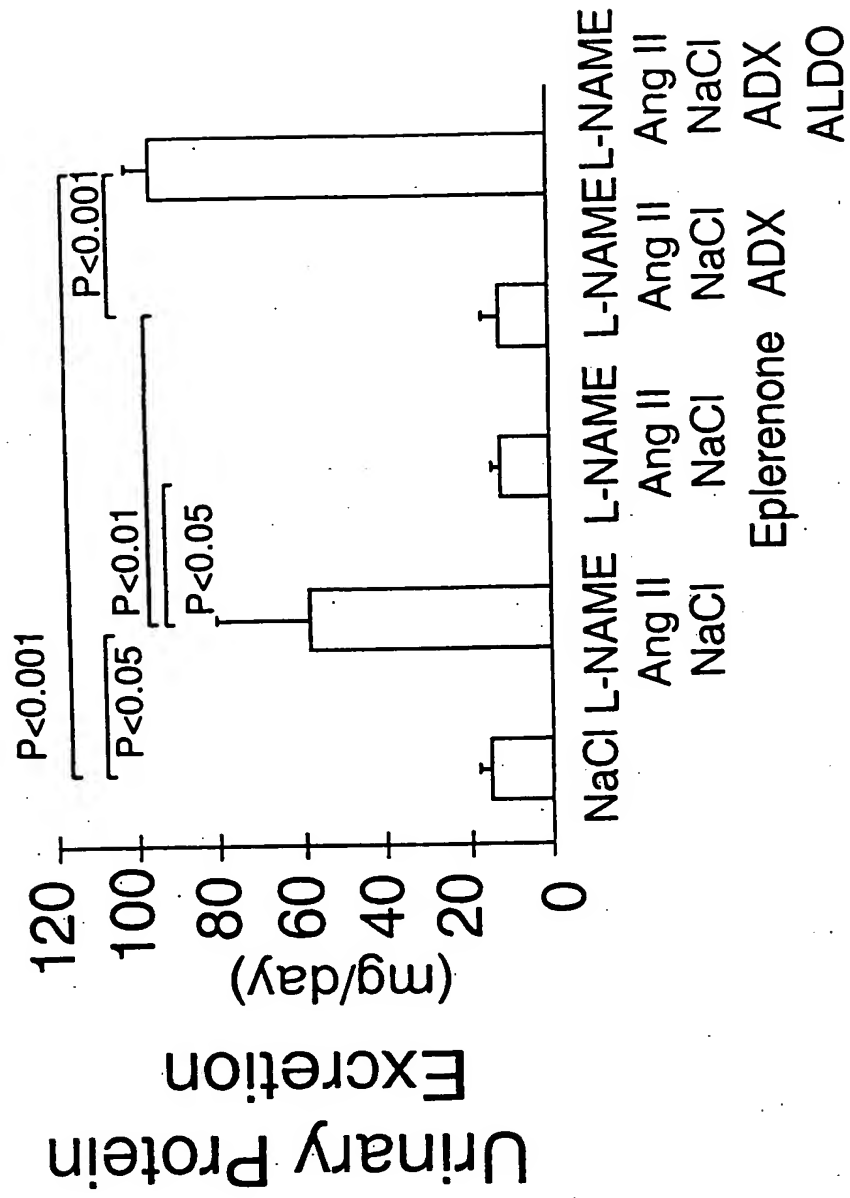


D





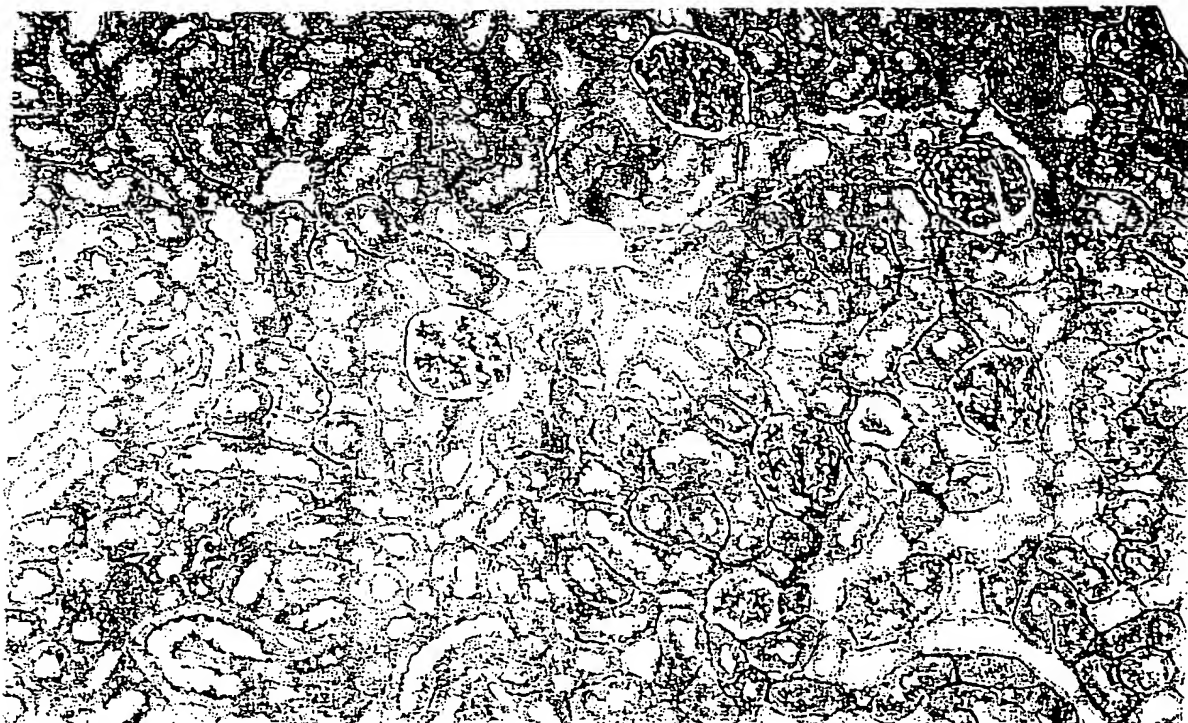
**Figure A-4. Histopathologic scores for myocardial necrosis.**



**Figure A-5. Urinary protein excretion.**

FIGURE A-6

A



B

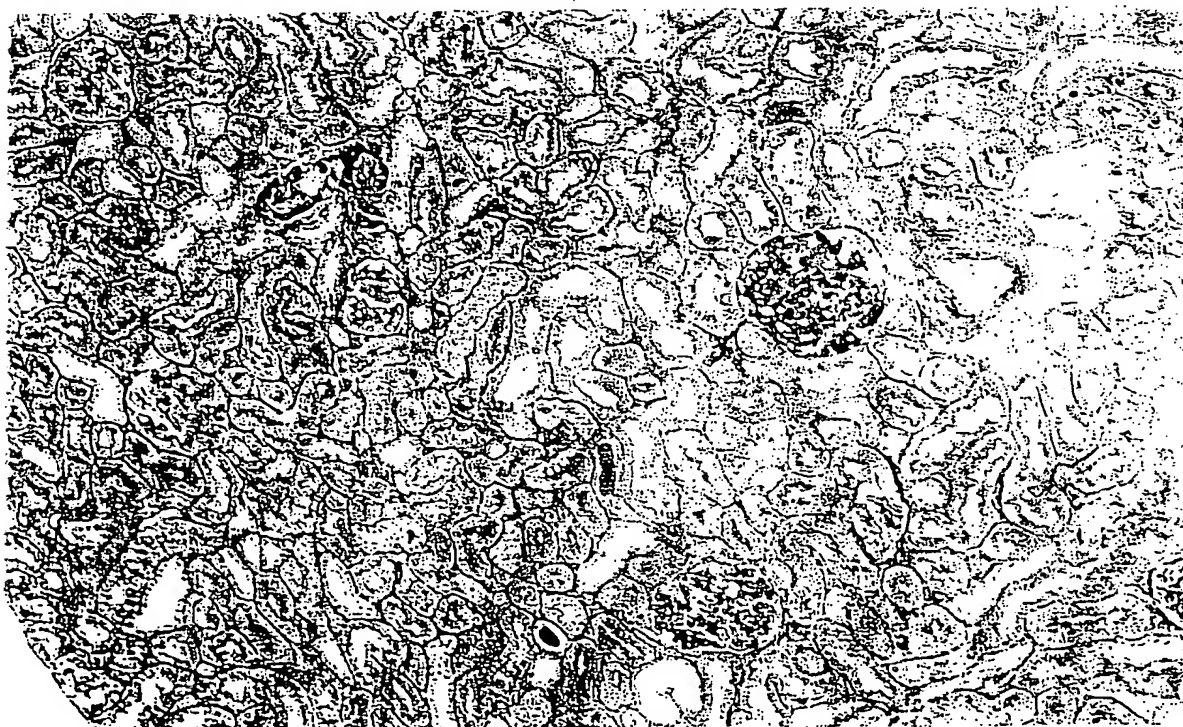
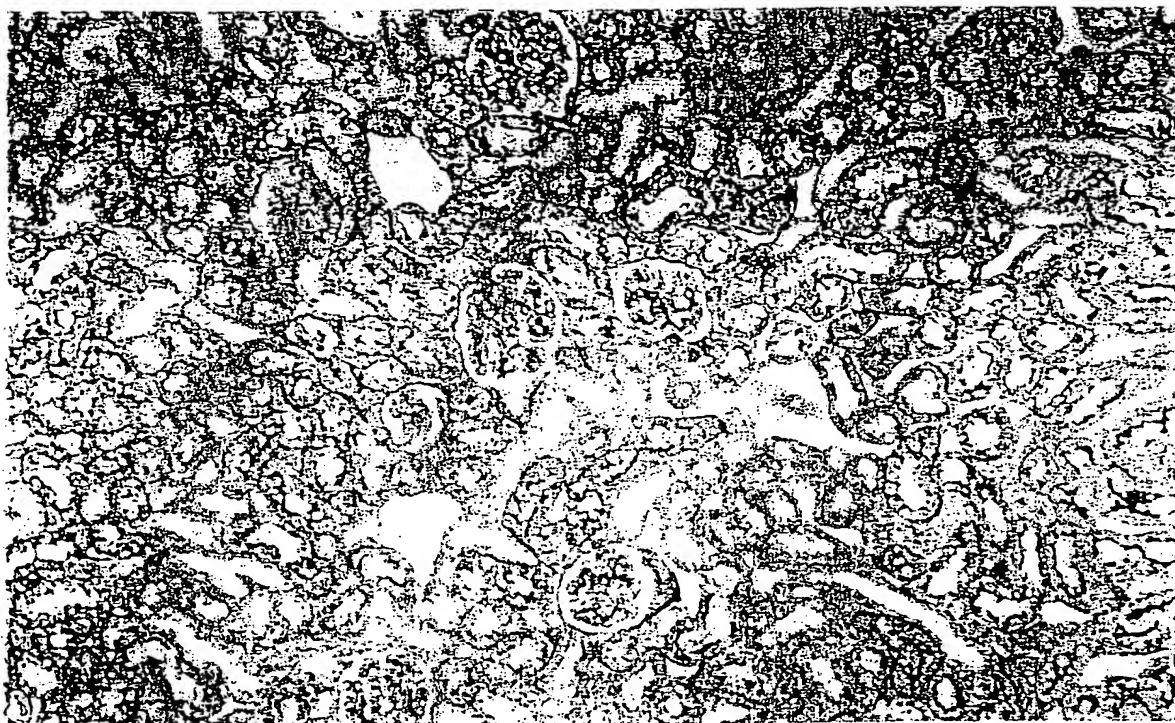
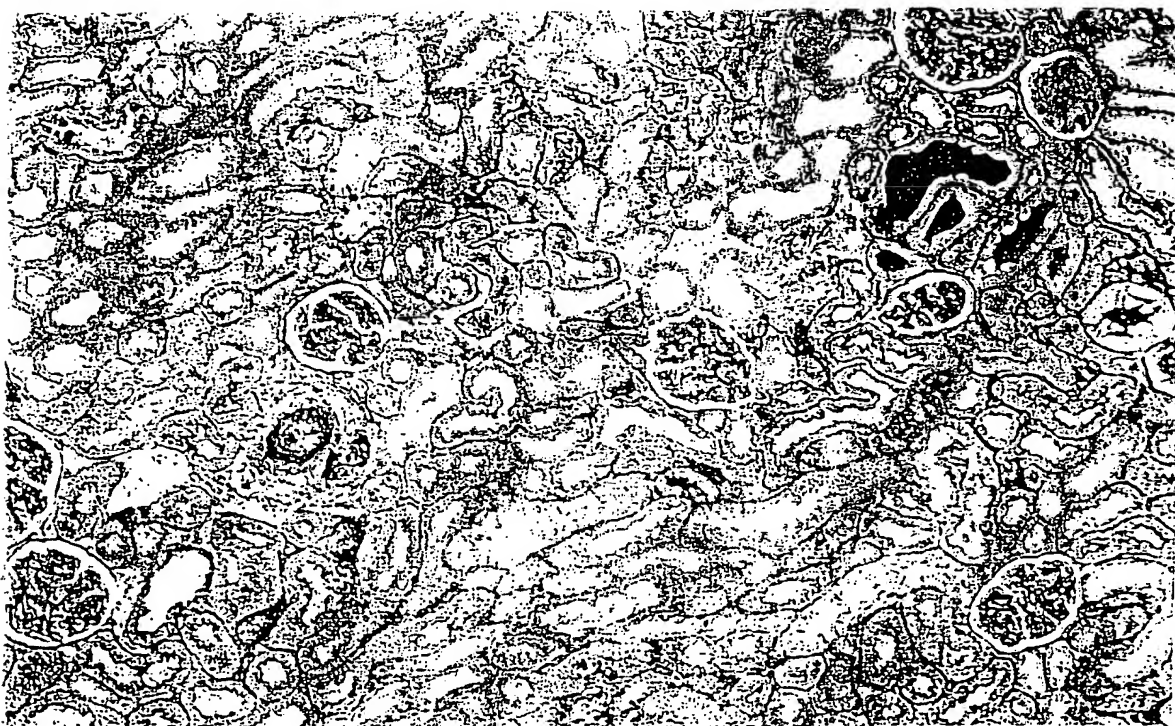


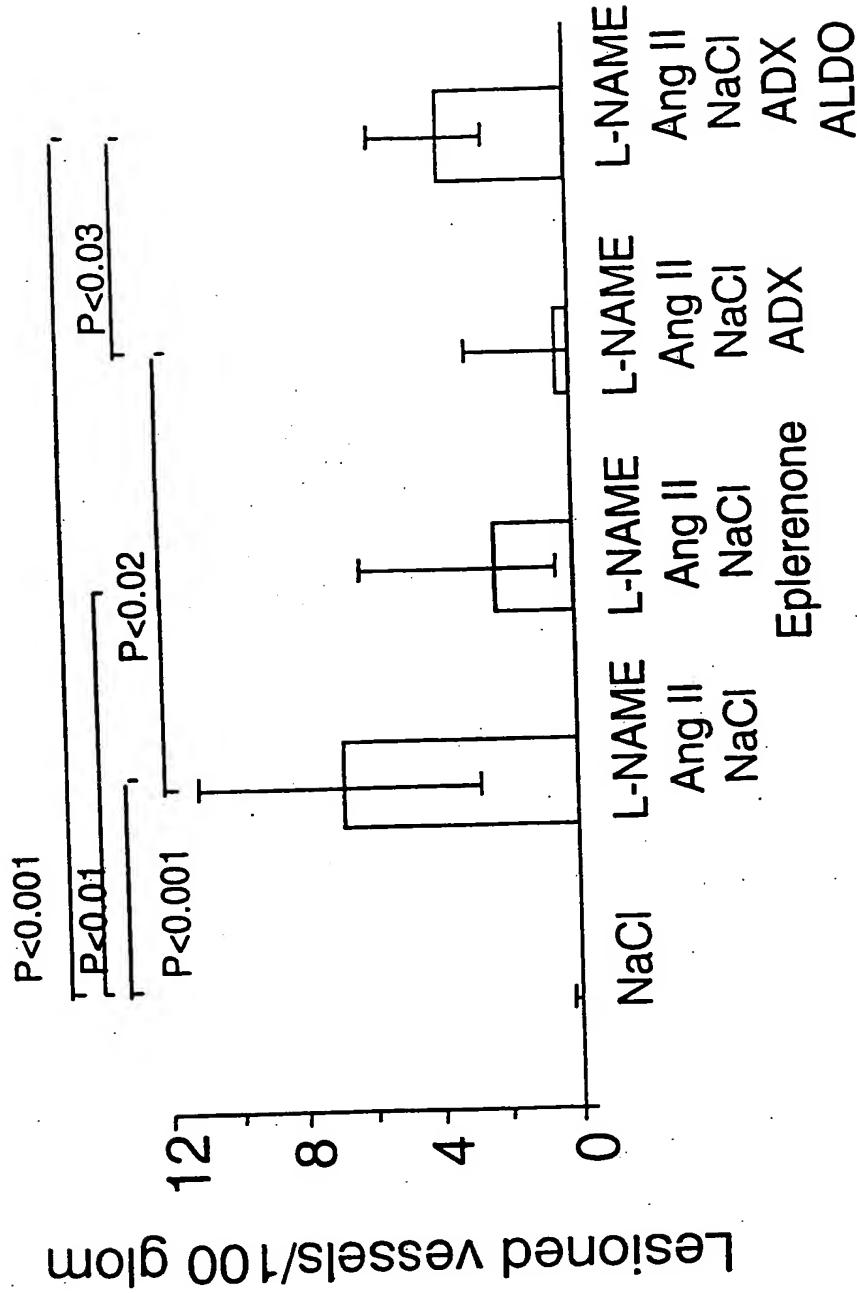
FIGURE A-6

C



D



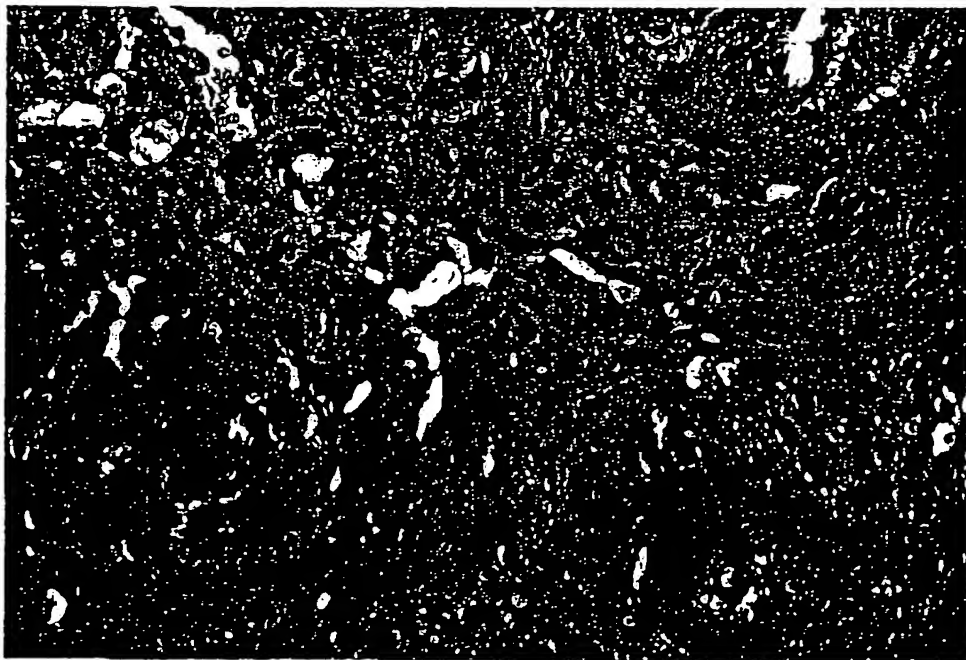


**Figure A-7. Histopathologic scores for renal vascular injury.**





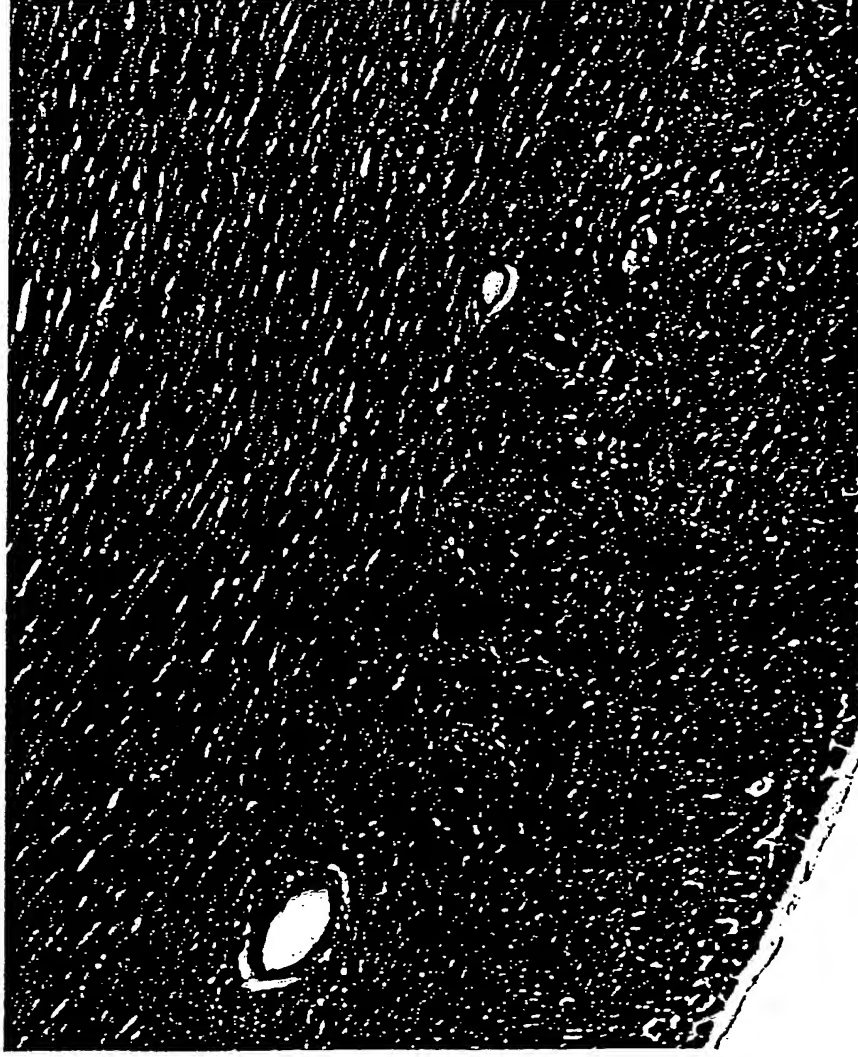
100X



400X

Fig. A-8 INFLAMMATORY LESIONS IN CORONARY ARTERIES OF  
ALDOSTERONE/SALT UNINEPHRECTOMIZED RATS

Eplerenone-Treated Rat



100X

Fig. A-9 INFLAMMATORY LESIONS IN EPLERENONE - TREATED  
CORONARY ARTERIES OF ALDOSTERONE/SALT UNINEPHRECTOMIZED RATS



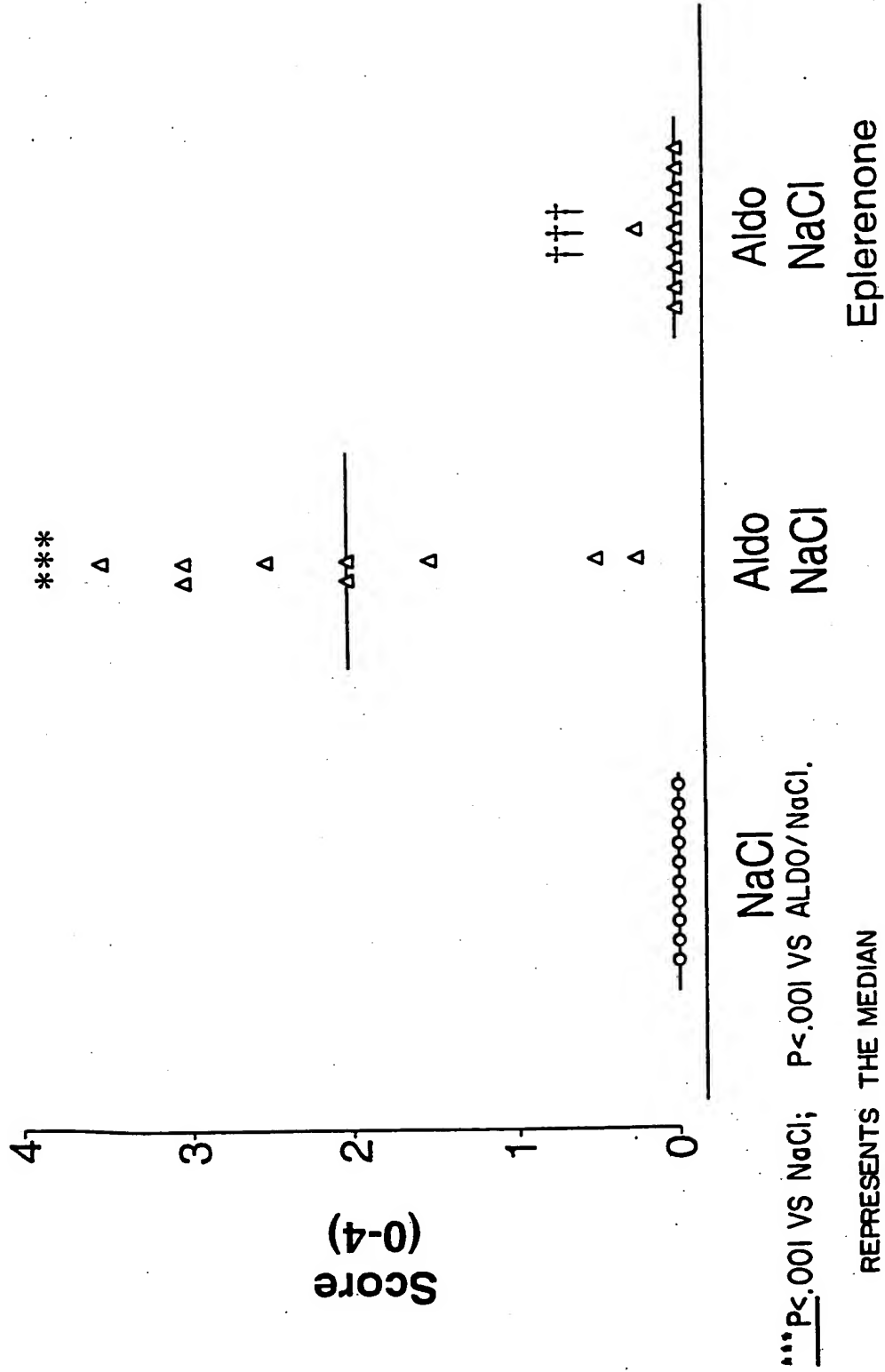


Fig. A-10: Myocardial Injury in Aldosterone/Salt Uninephrectomized Rats

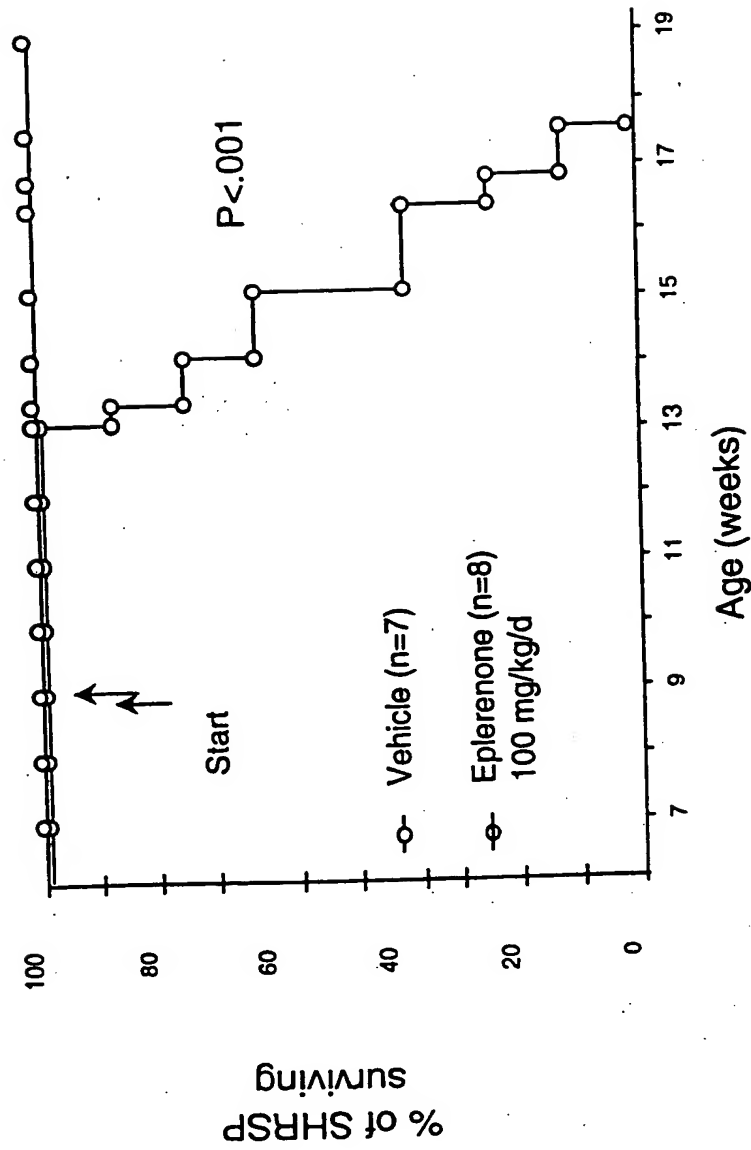
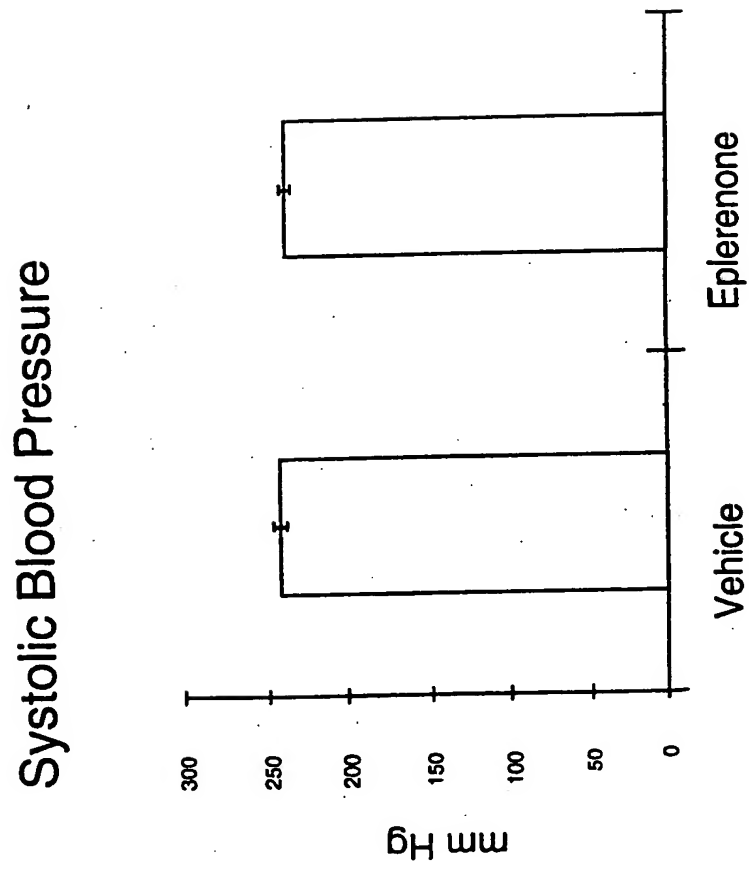


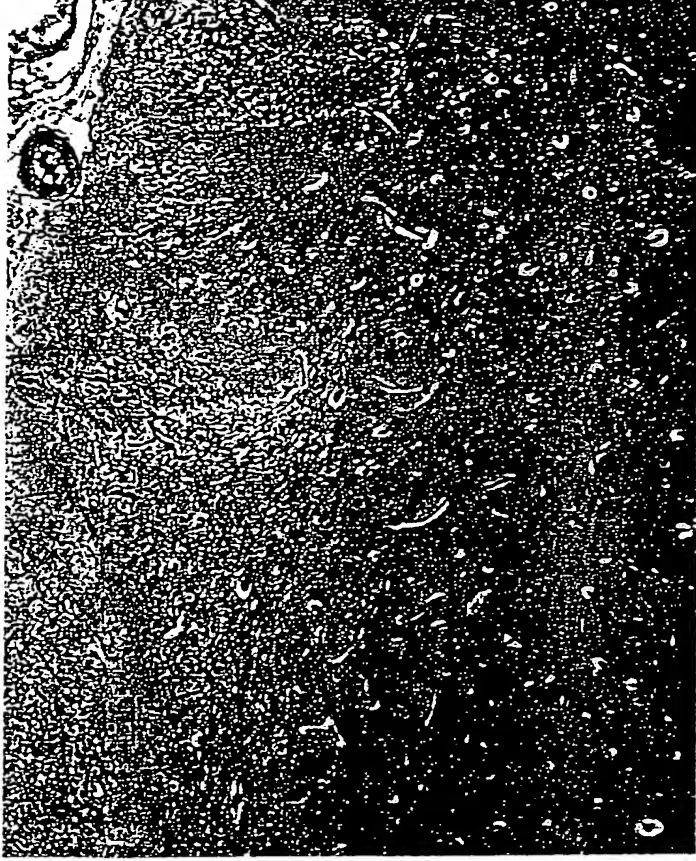
Fig. A-11: Survival in Saline-Drinking Stroke-Prone SHR Rats



**Fig. A-12: SBP in Saline-Drinking Stroke-Prone SHR Rats**



Vehicle-Treated  
SHRSP



Eplerenone-Treated  
SHRSP

Fig. A-13: Cerebral Injury in Saline-Drinking Stroke-  
Prone SHR Rats

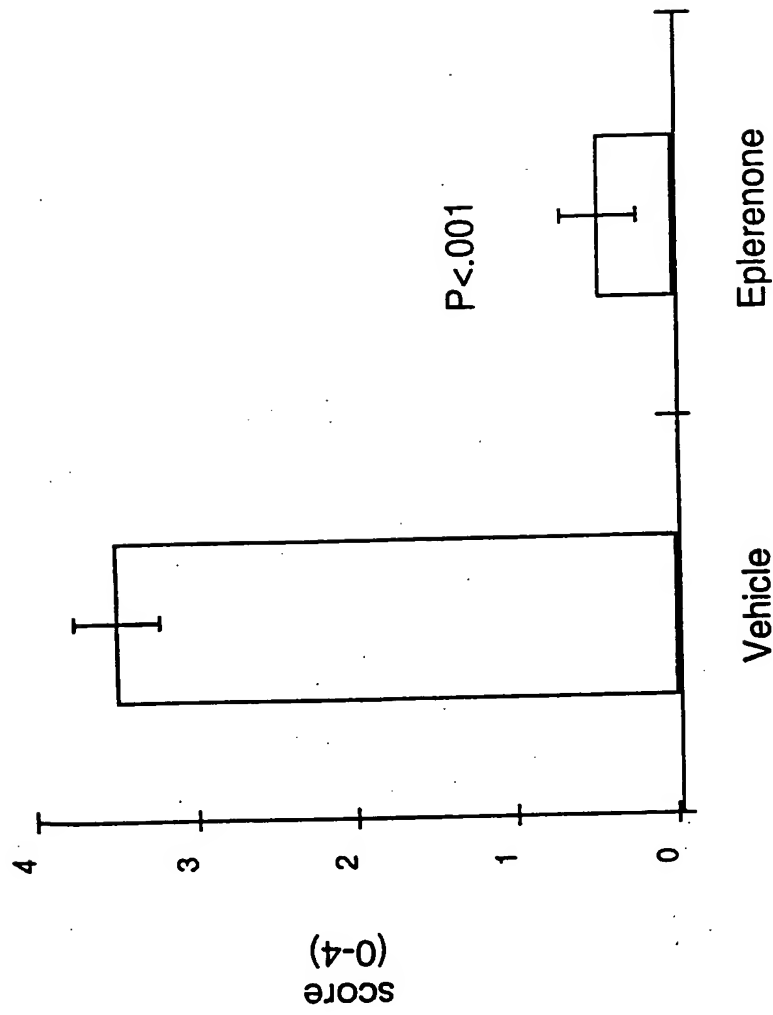


Fig. A-14: Cerebral Injury in Saline-Drinking Stroke-Prone SHR Rats

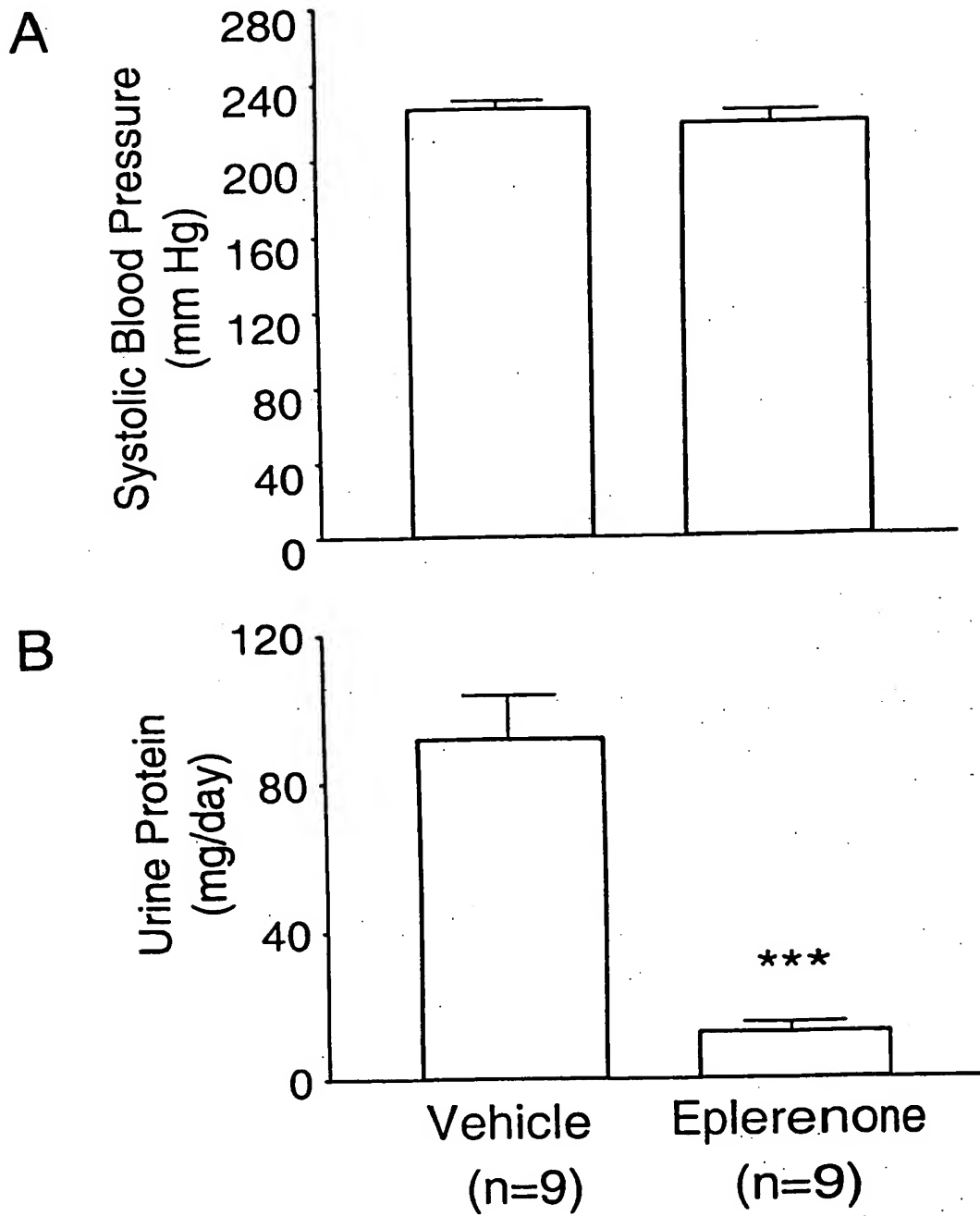
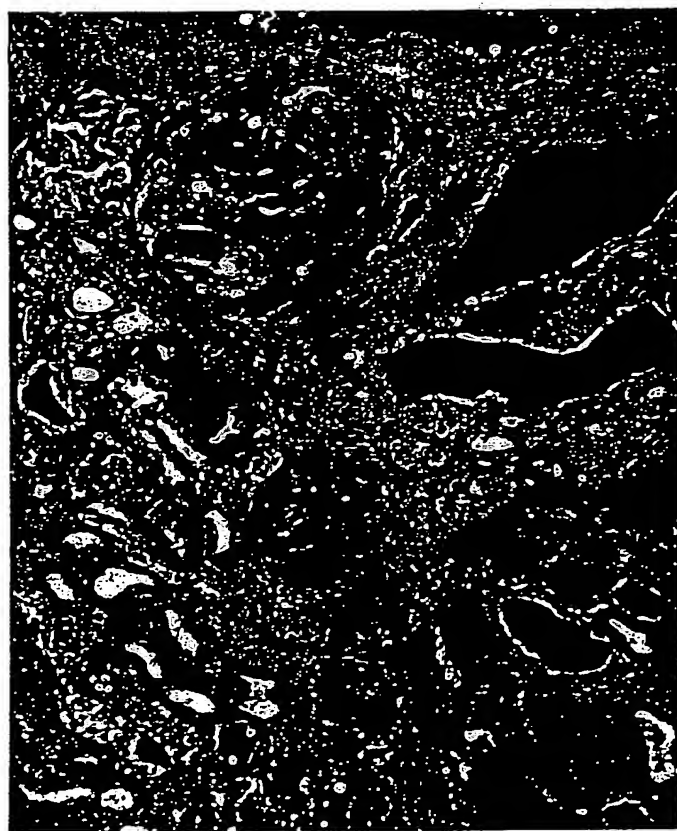


Fig. A-15

Fig. A-16

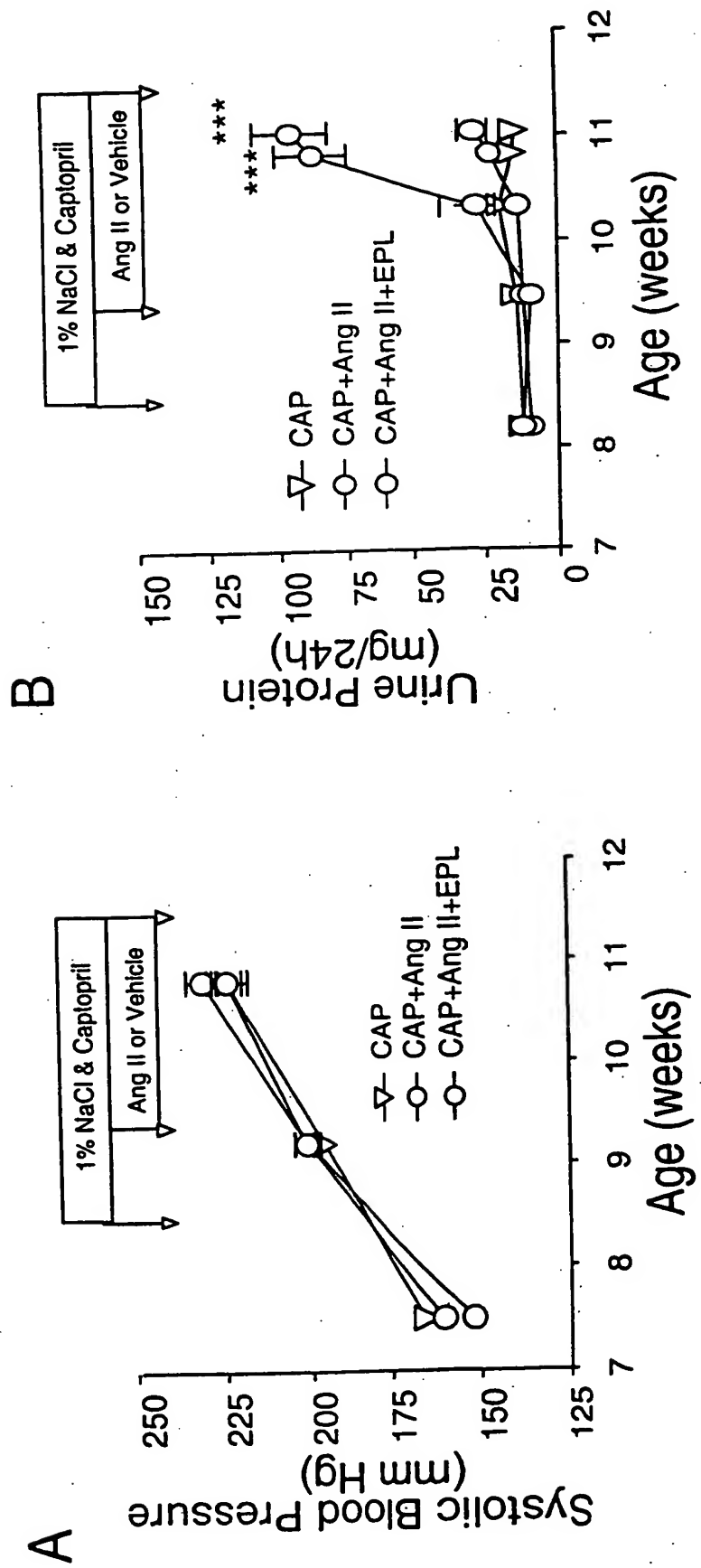


A



B

Fig. A-17





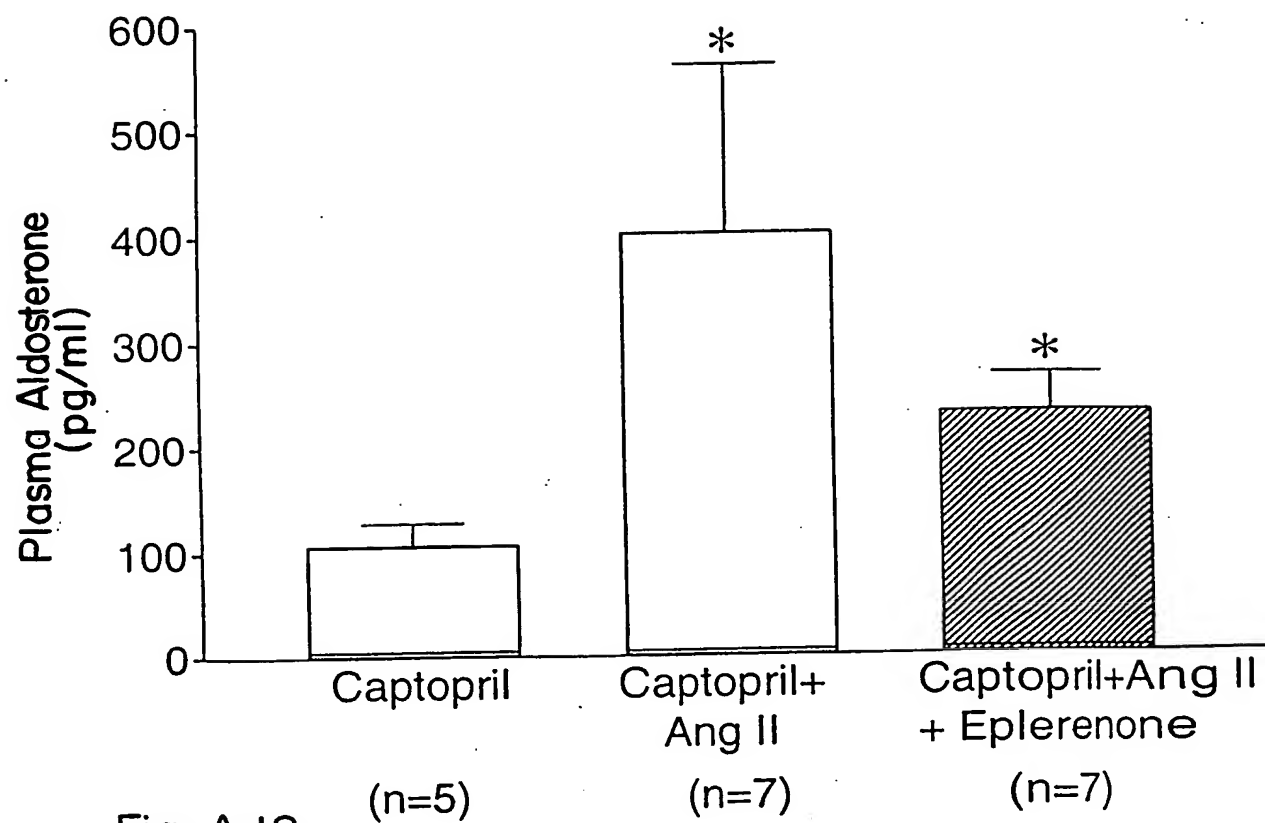


Fig. A-18

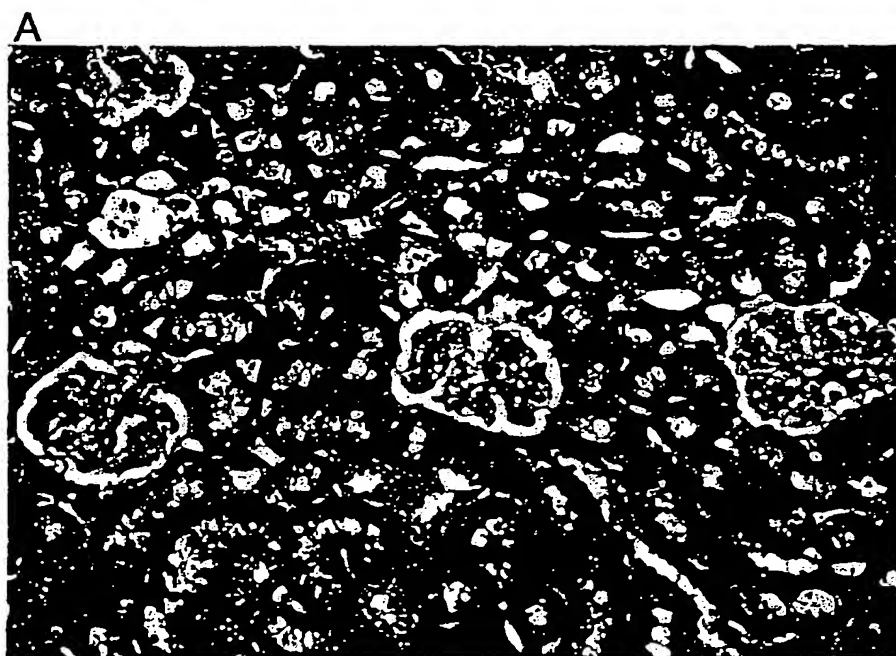
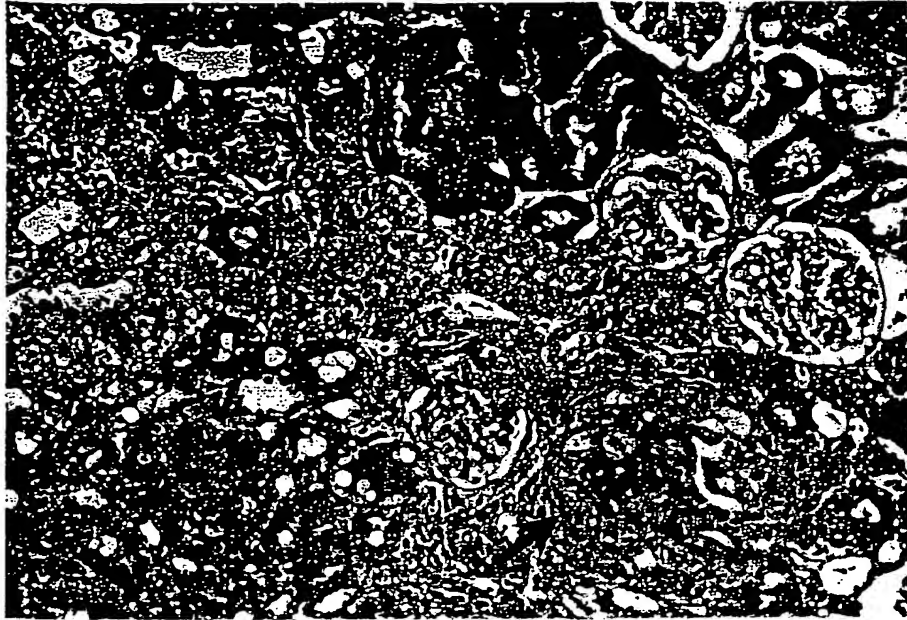


Fig. A-19

B



C

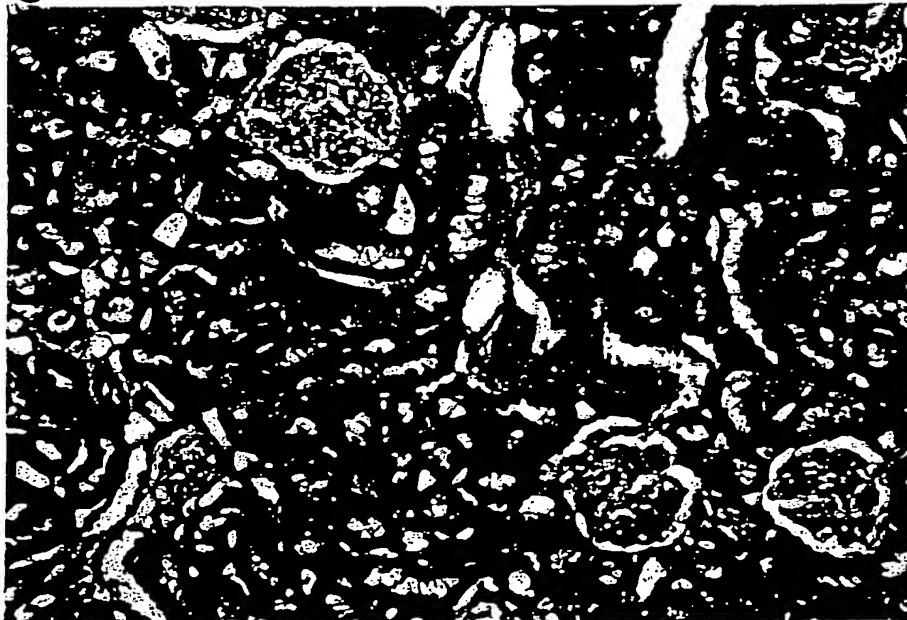


Fig. A-19 Cont'd.

# Population Effect on PK Profile of SC-66110

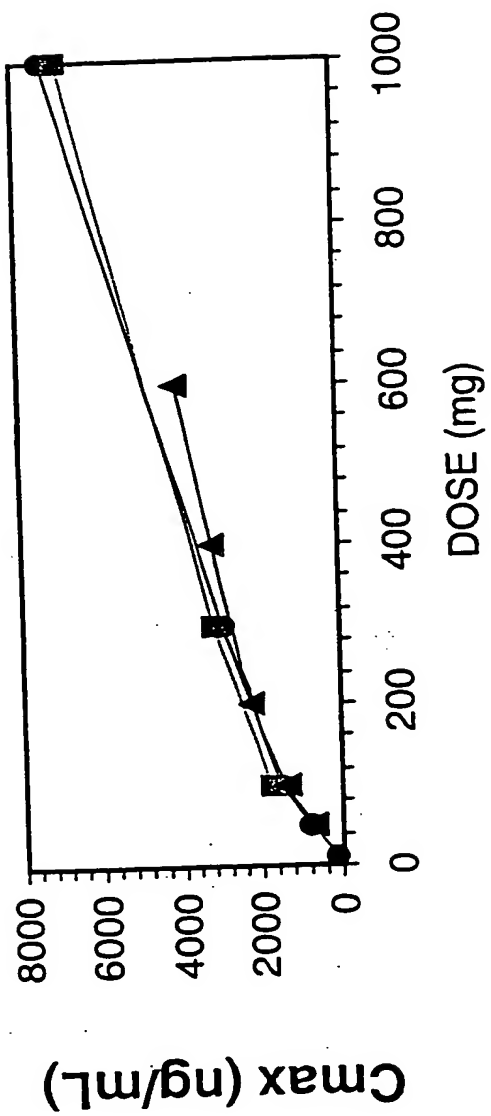


Figure A-20

# Population Effect on PK Profile of SC-66110

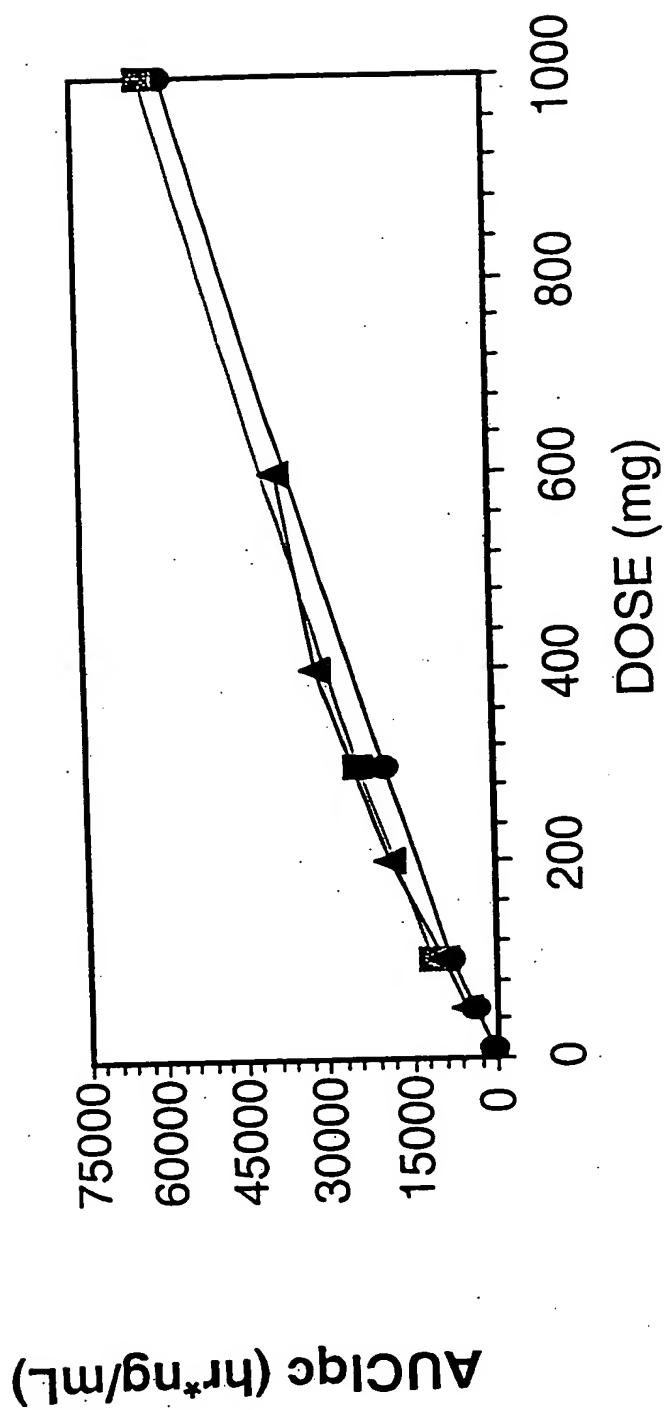
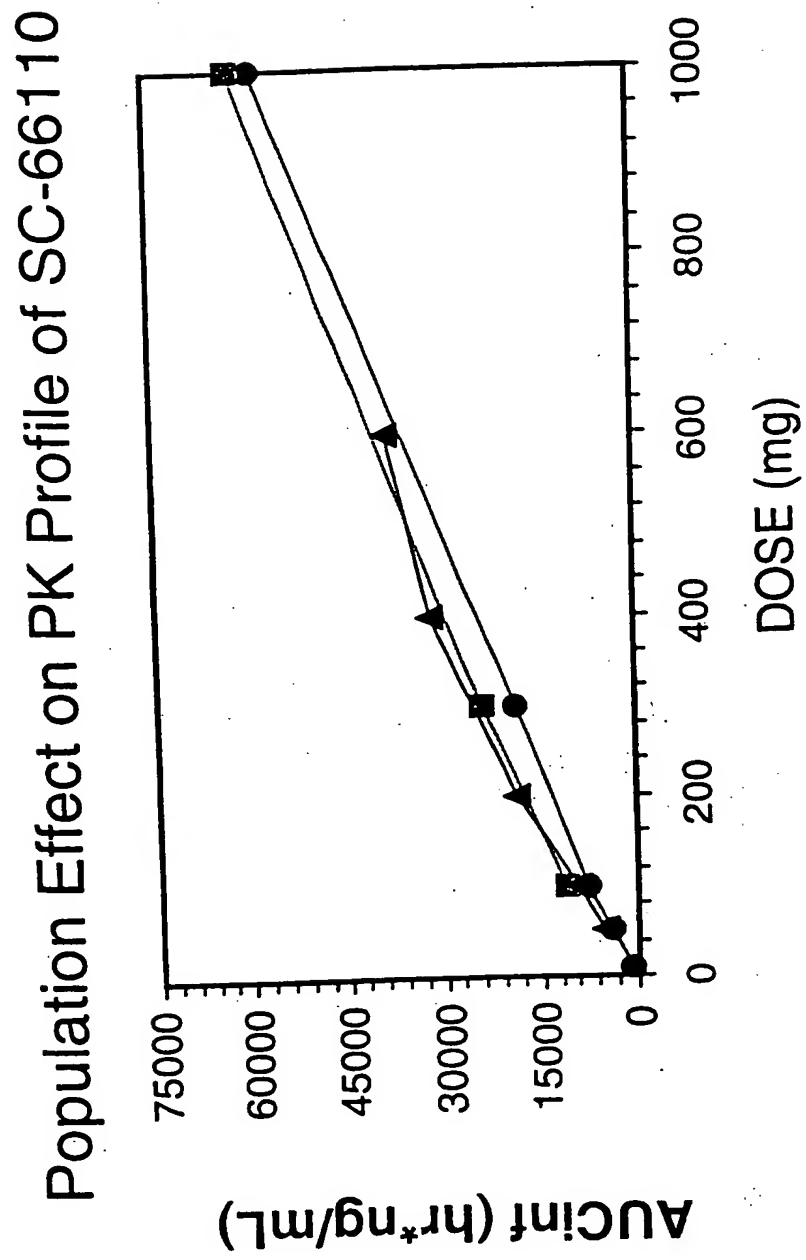


Figure A-21

**Figure A-22**

## Population Effect on PK Profile of SC-66110

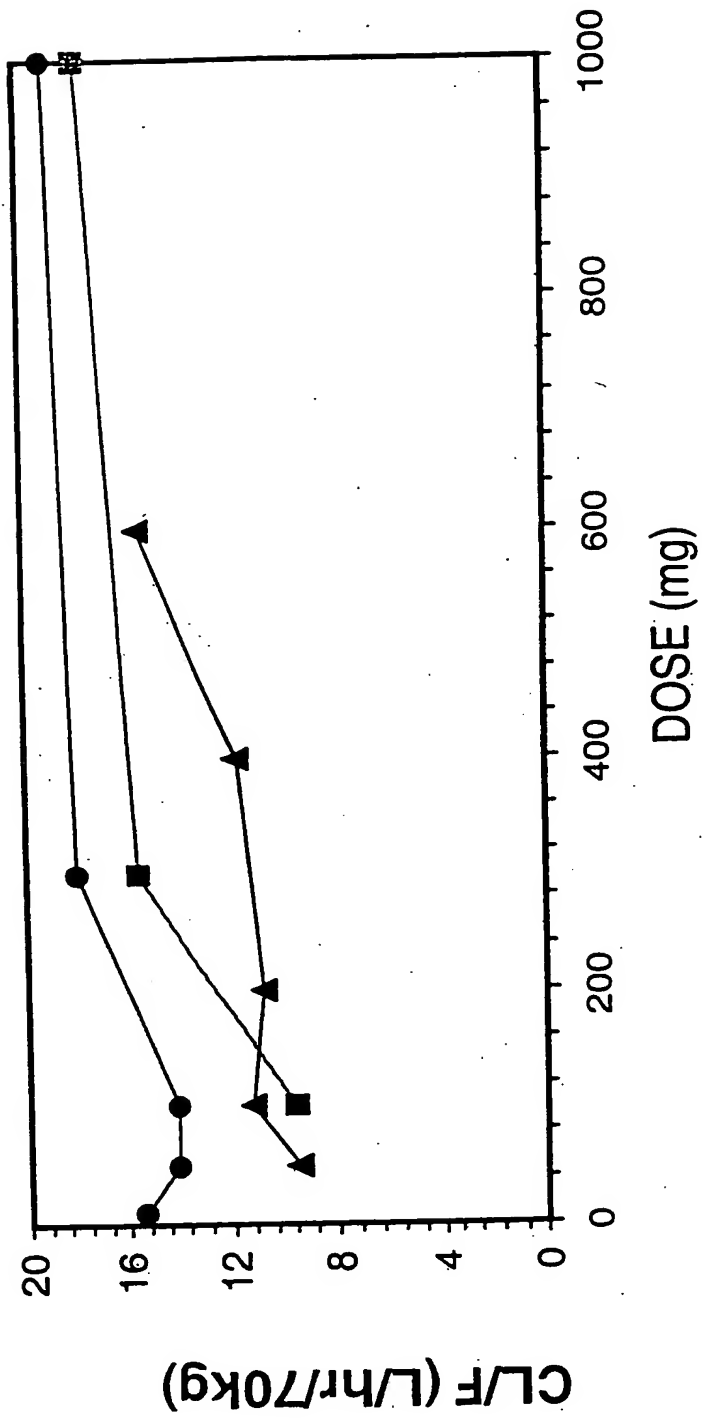


Figure A-23

# Population Effect on PK Profile of SC-66110

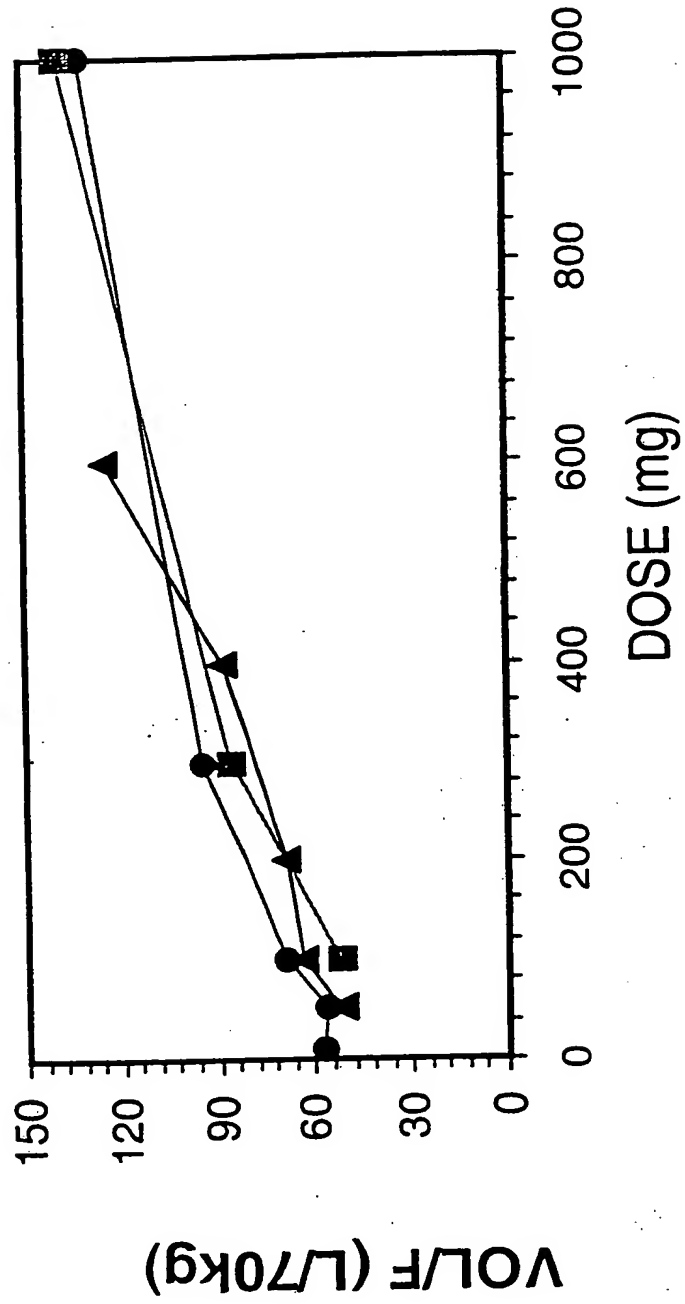


Figure A-24

## Population Effect on PK Profile of SC-70303

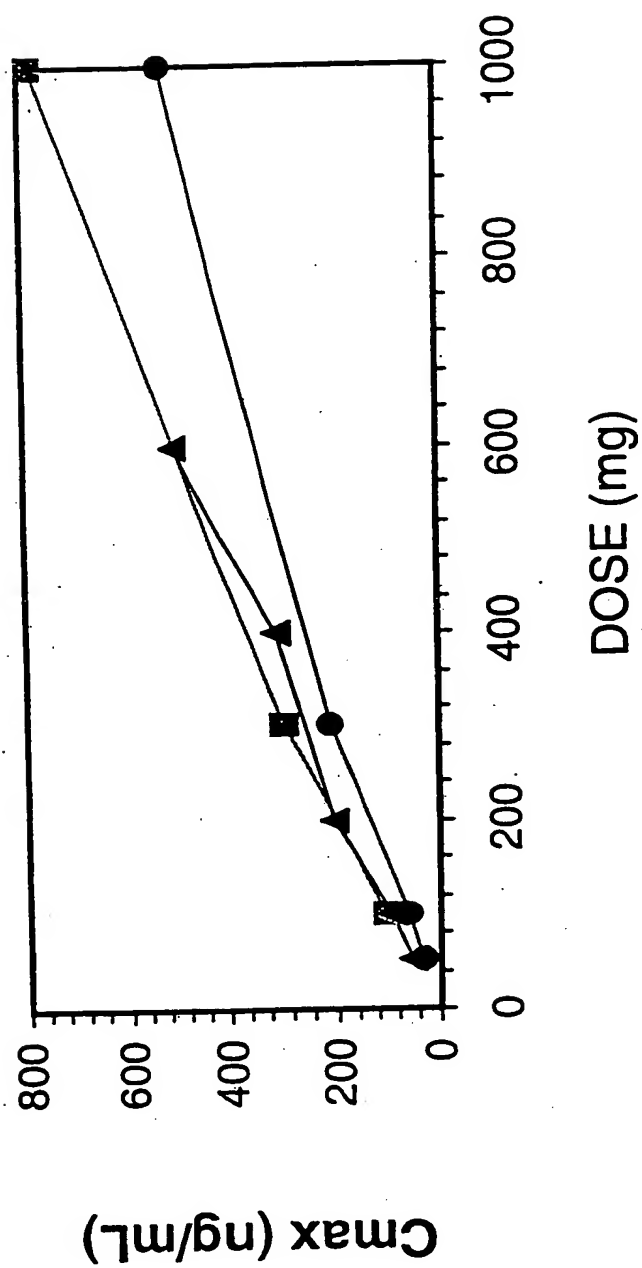


Figure A-25



# Population Effect on PK Profile of SC-70303

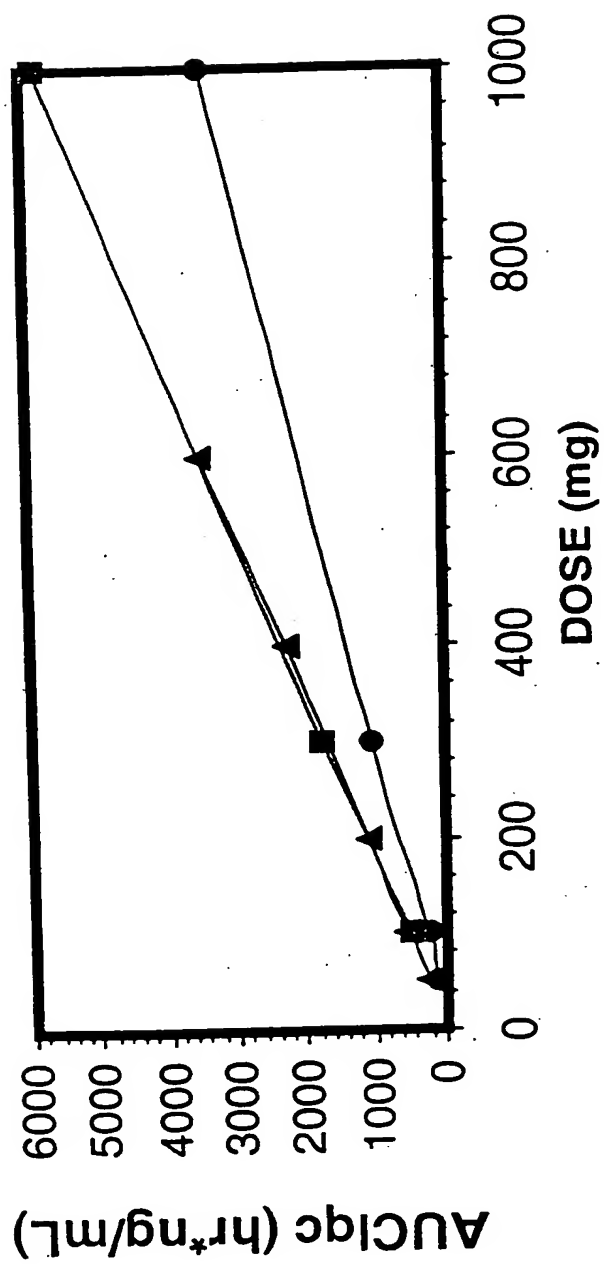


Figure A-26

# Population Effect on PK Profile of SC-70303

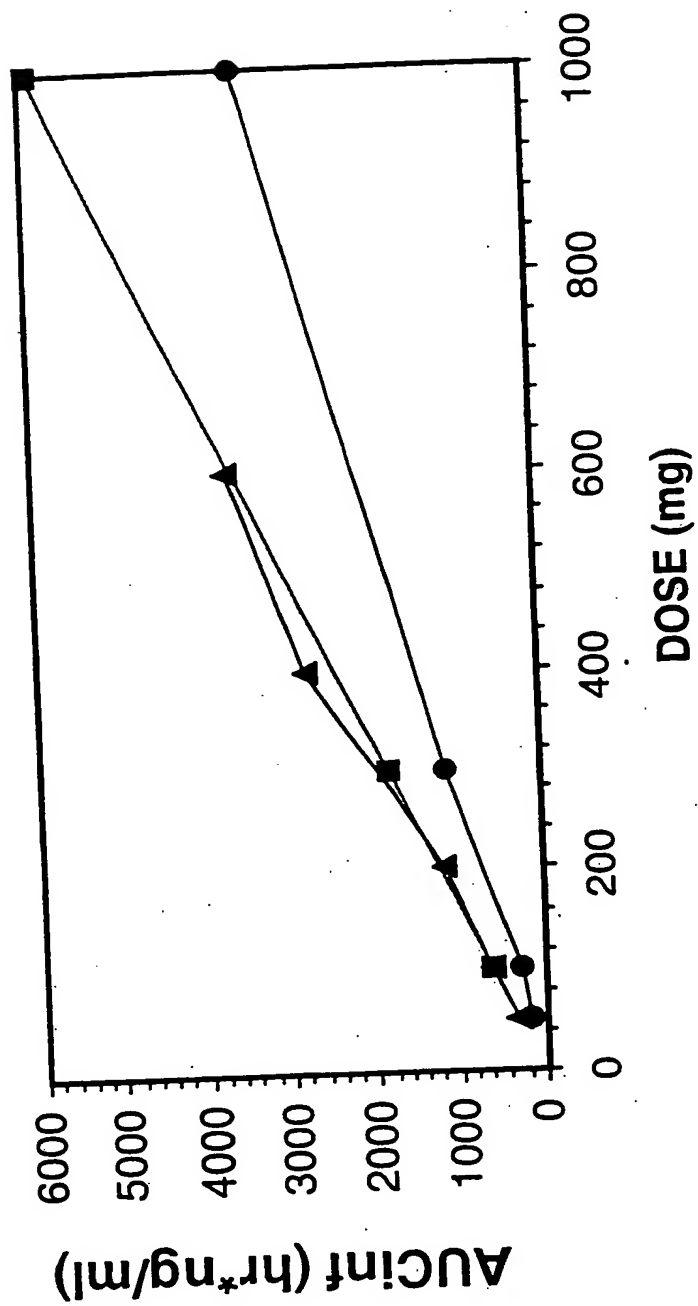


Figure A-27

# Population Effect on PK Profile of SC-70303

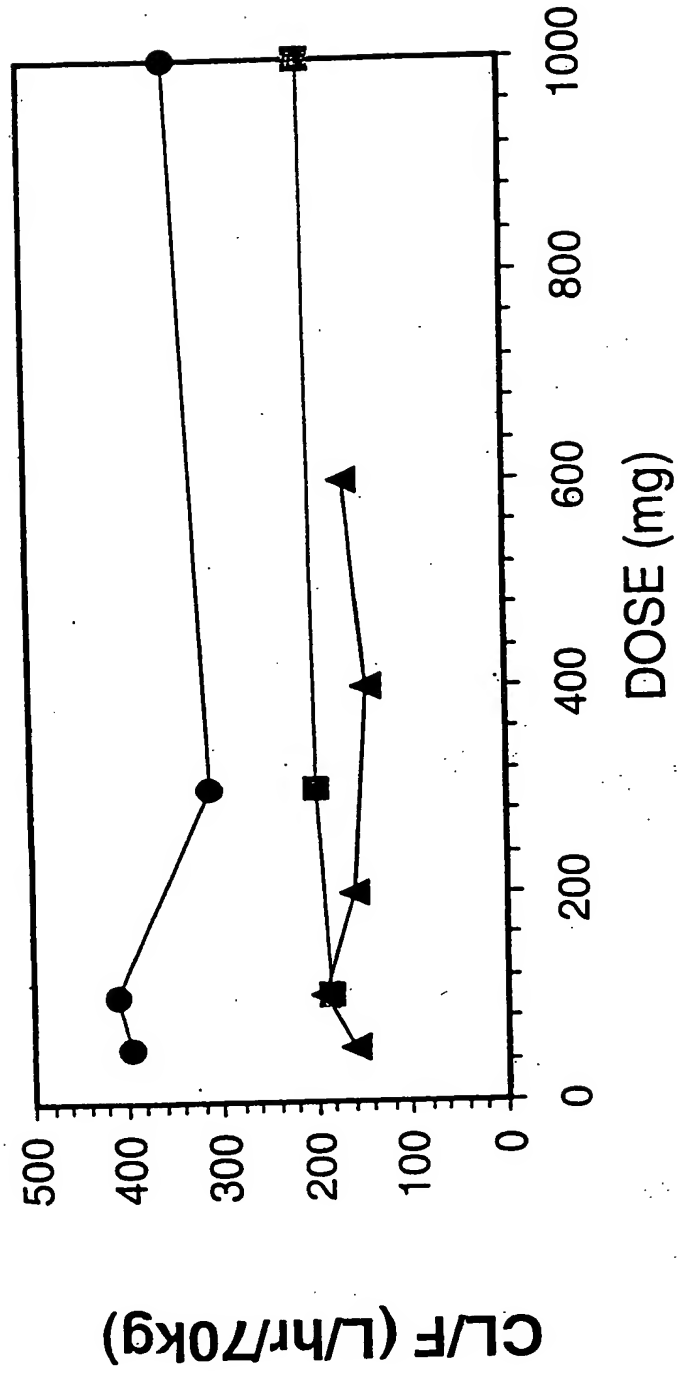


Figure A-28

# Population Effect on PK Profile of SC-70303

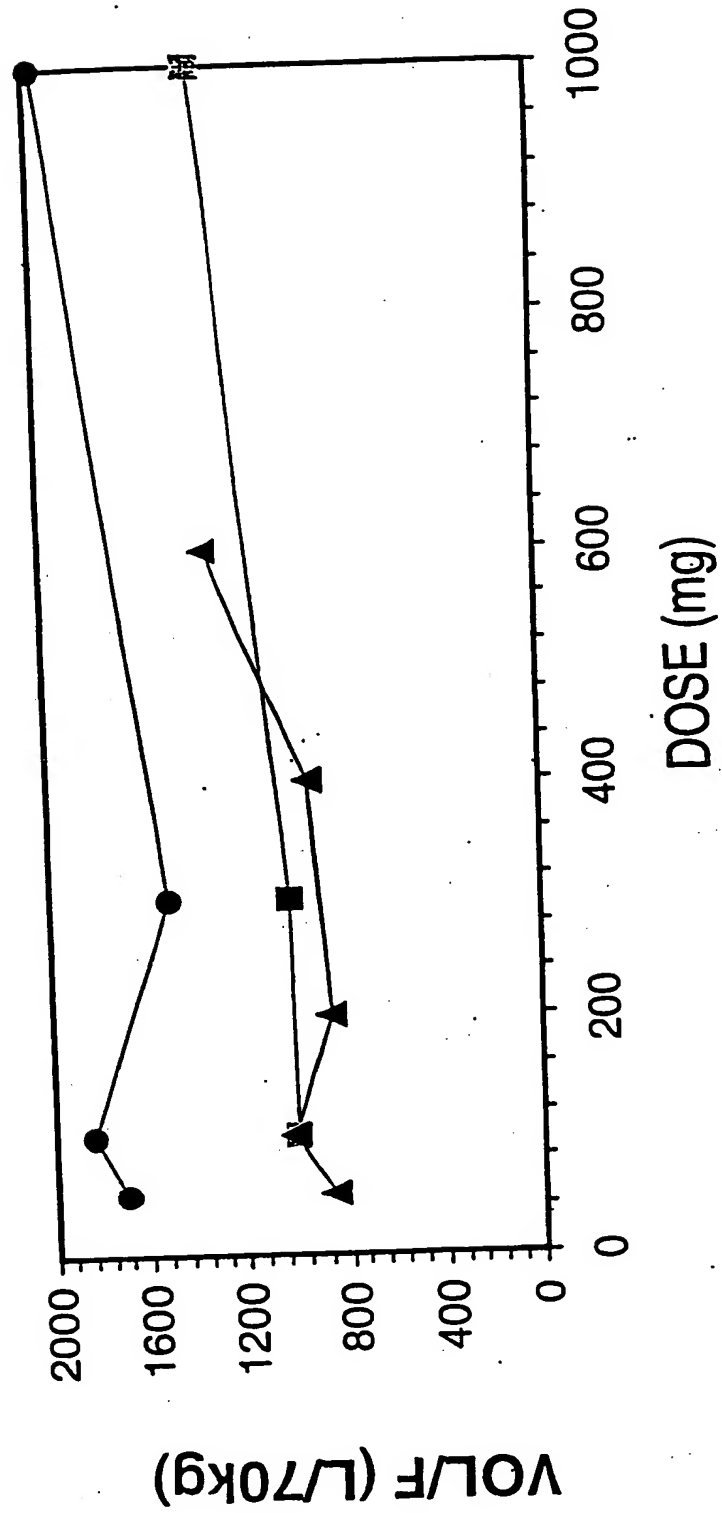


Figure A-29

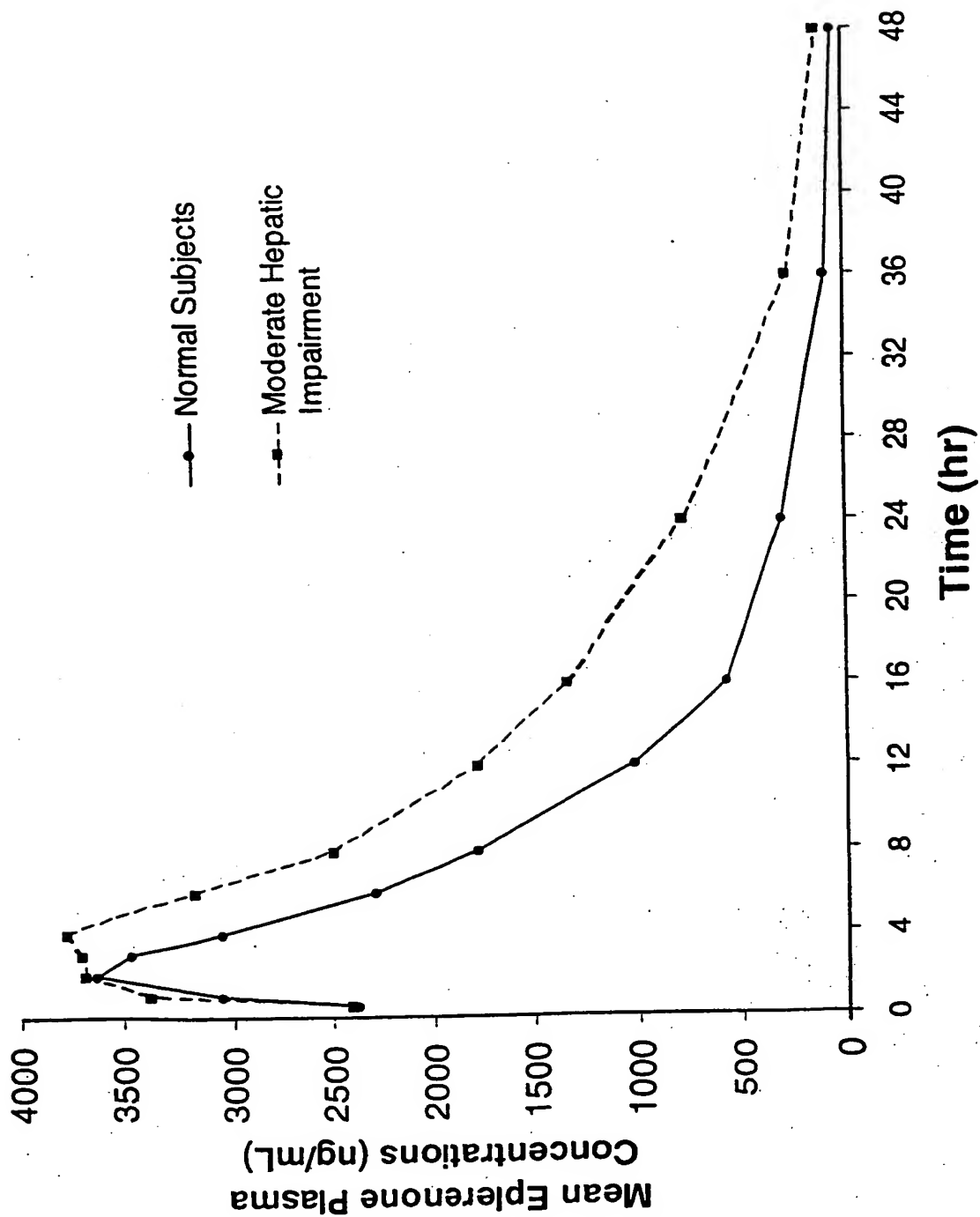


Figure A-30

FIGURE C-1

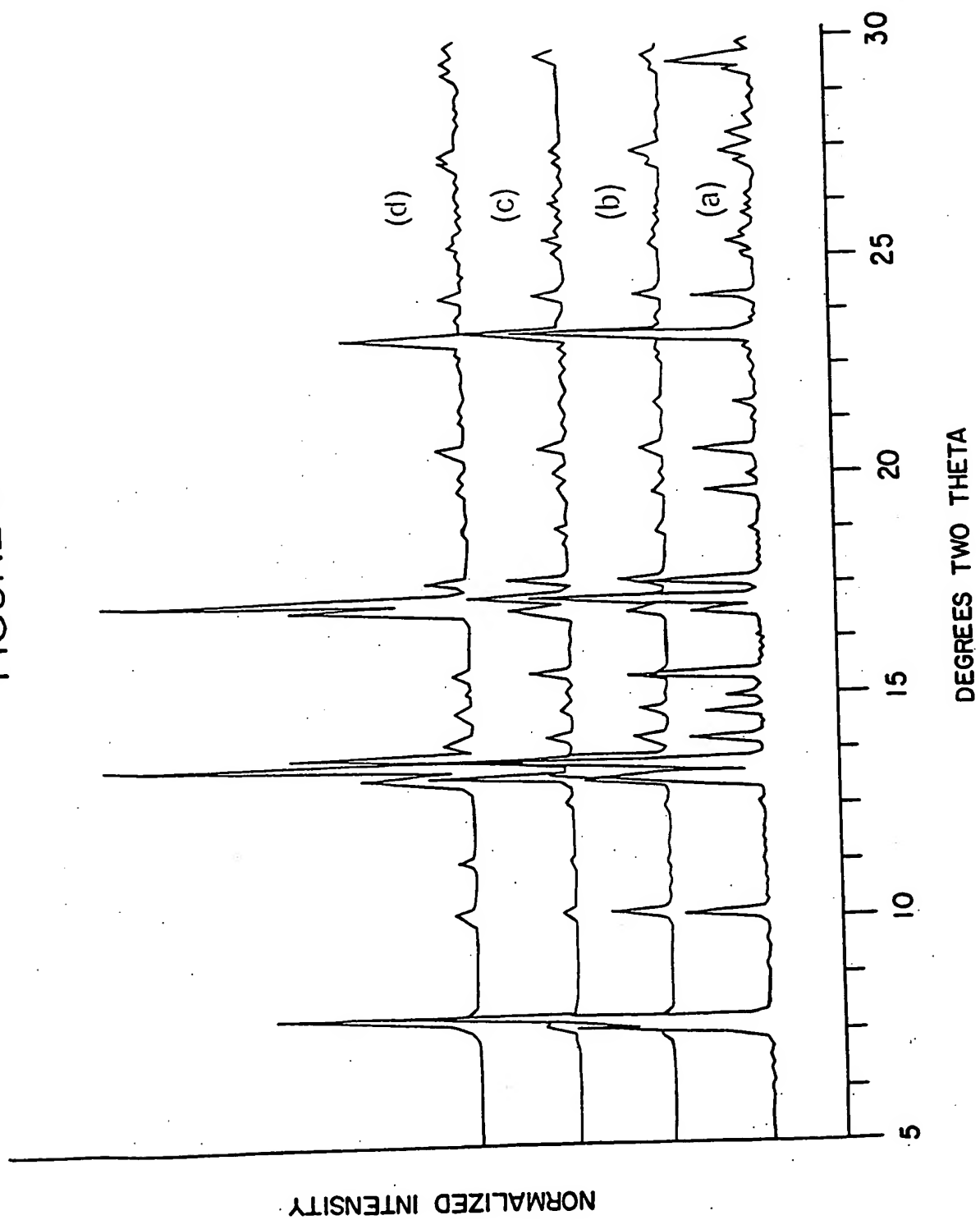


FIGURE C-2

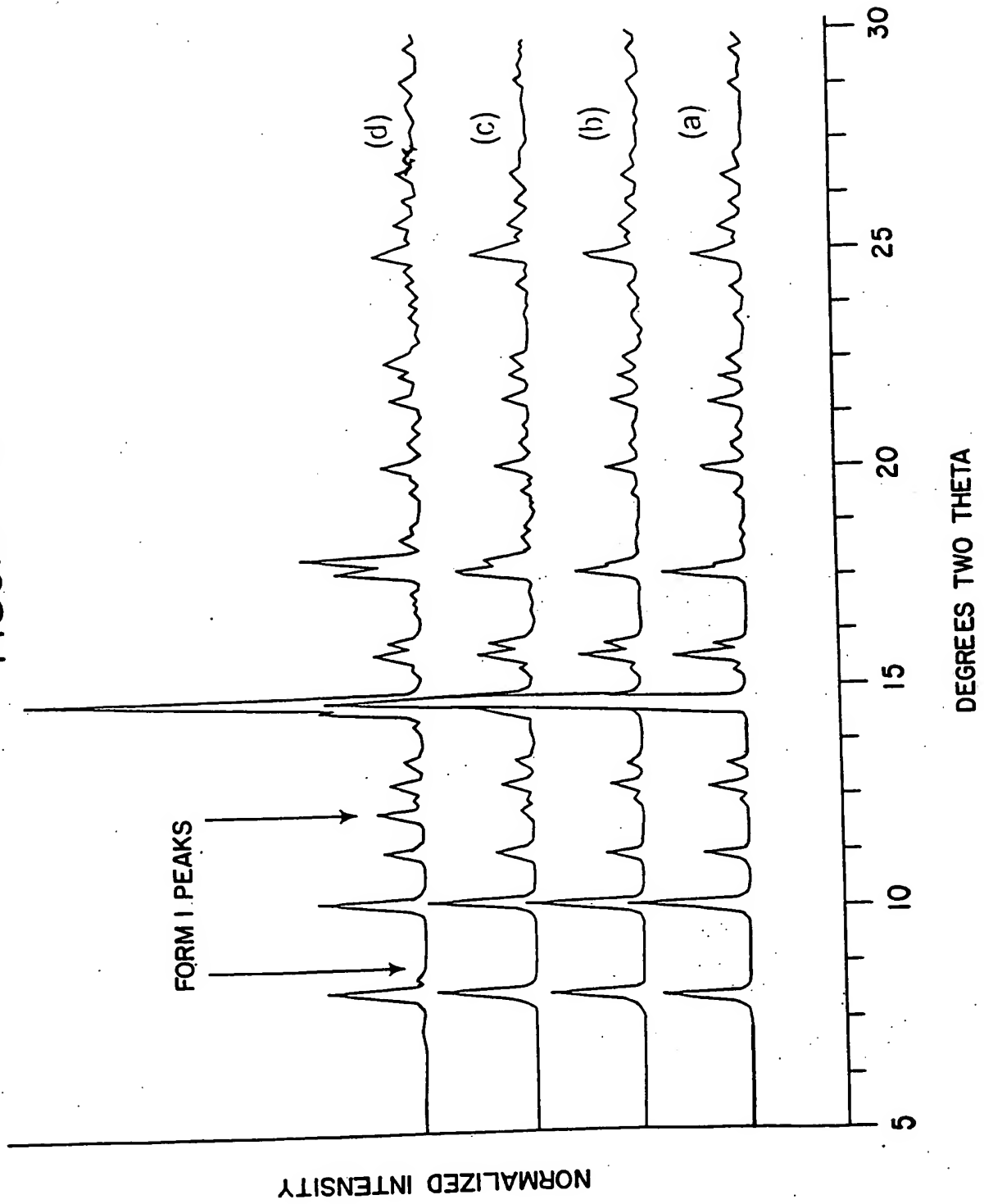


FIGURE C-3

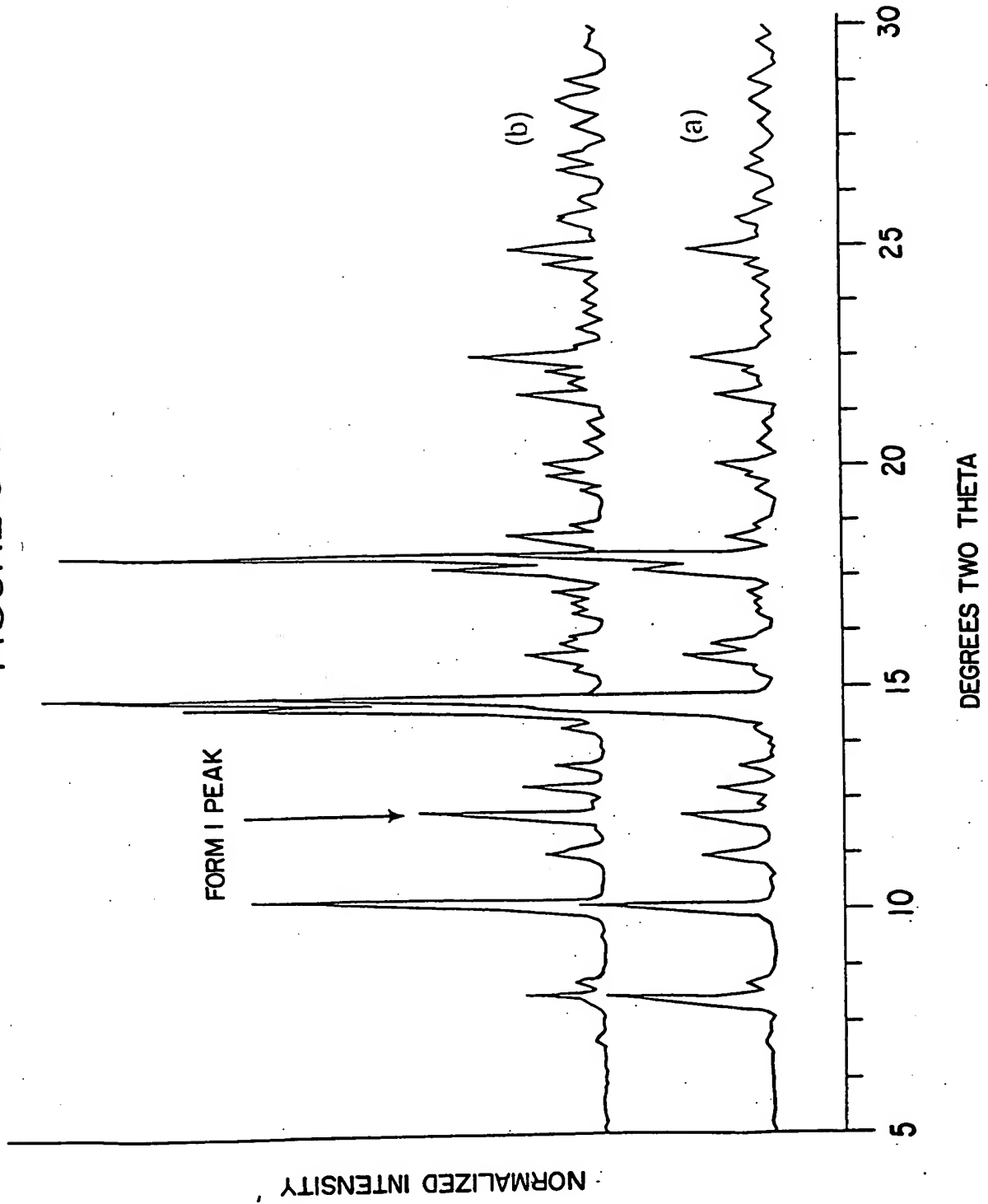




FIGURE C-4

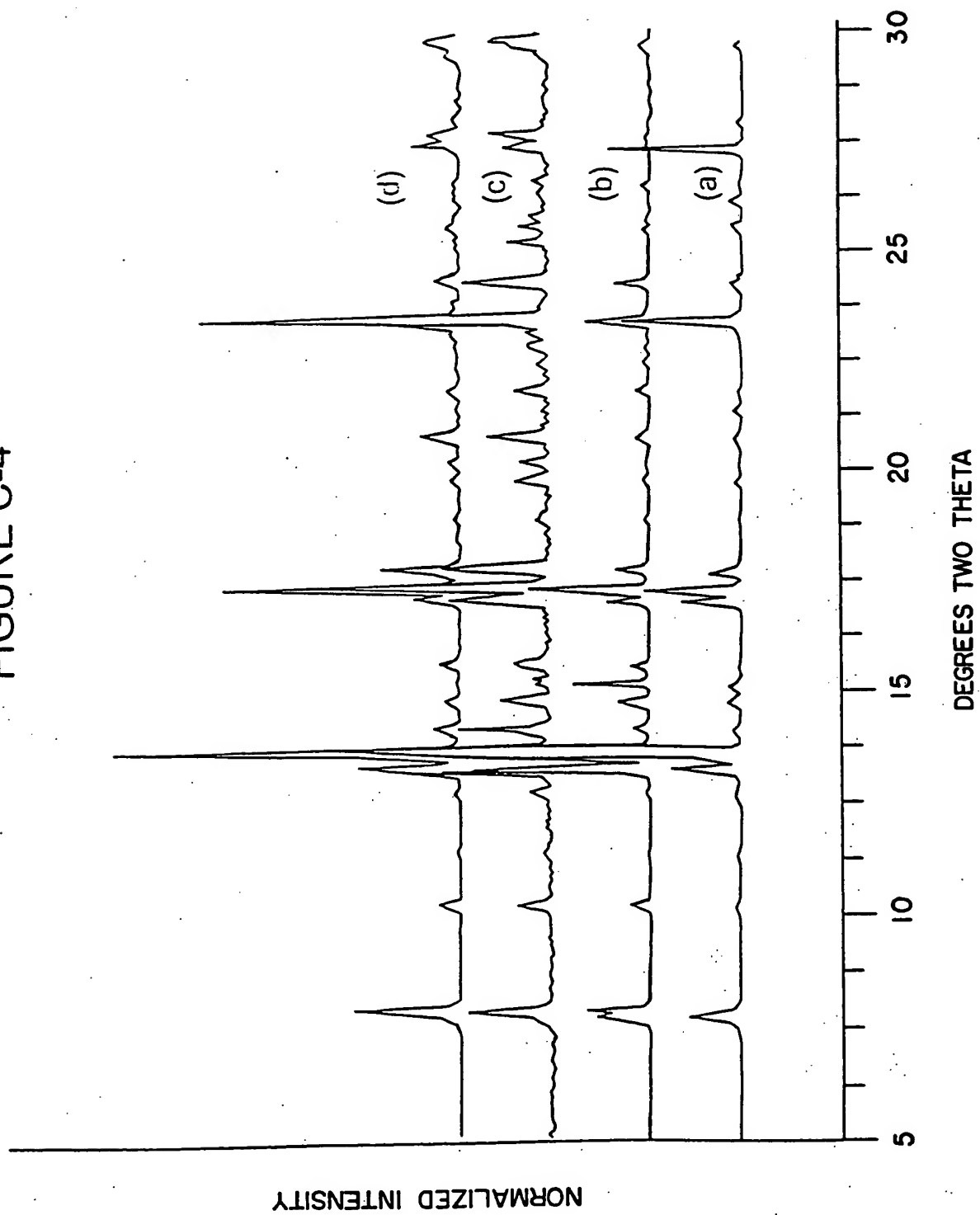


FIGURE C-5

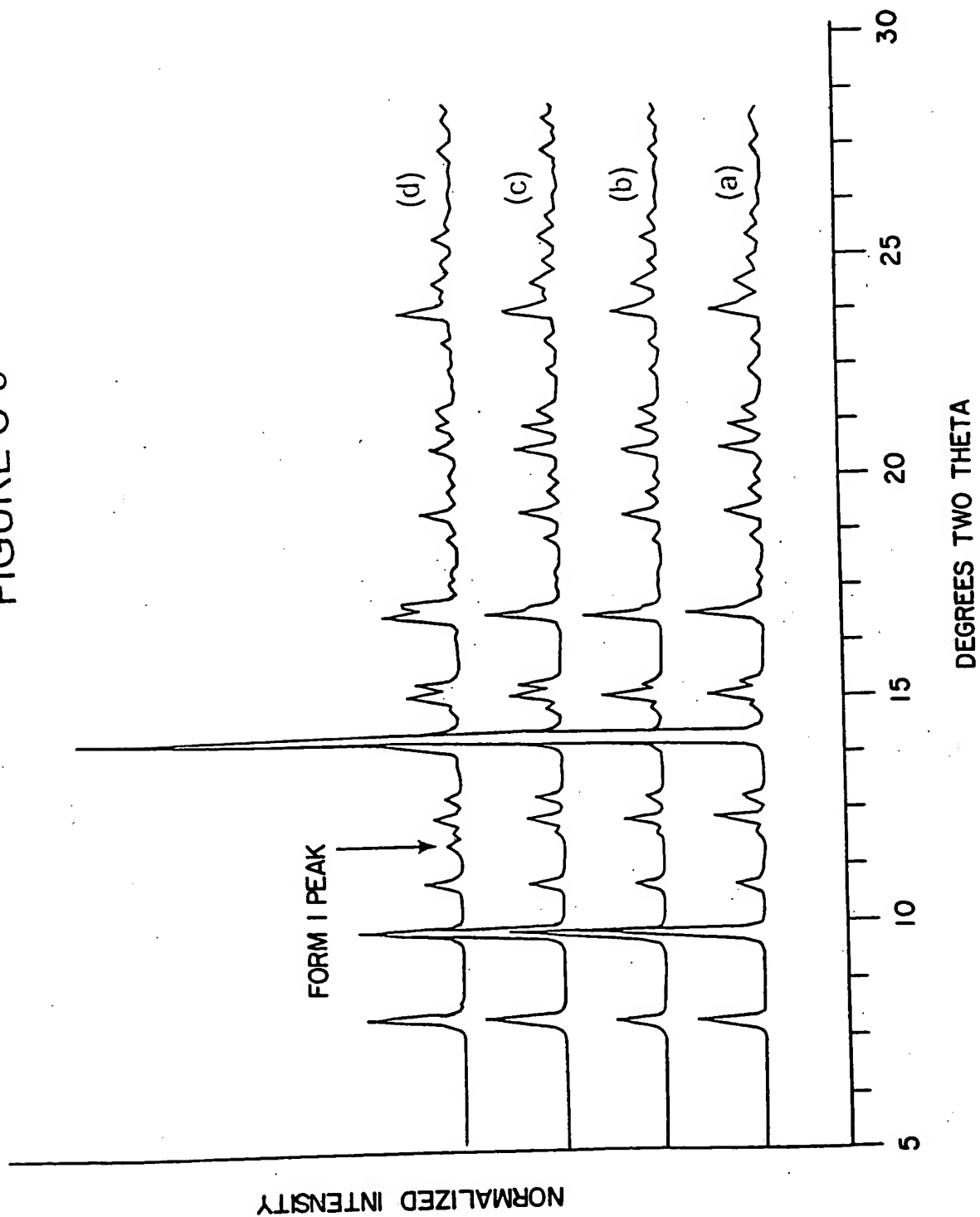


Fig. C-6

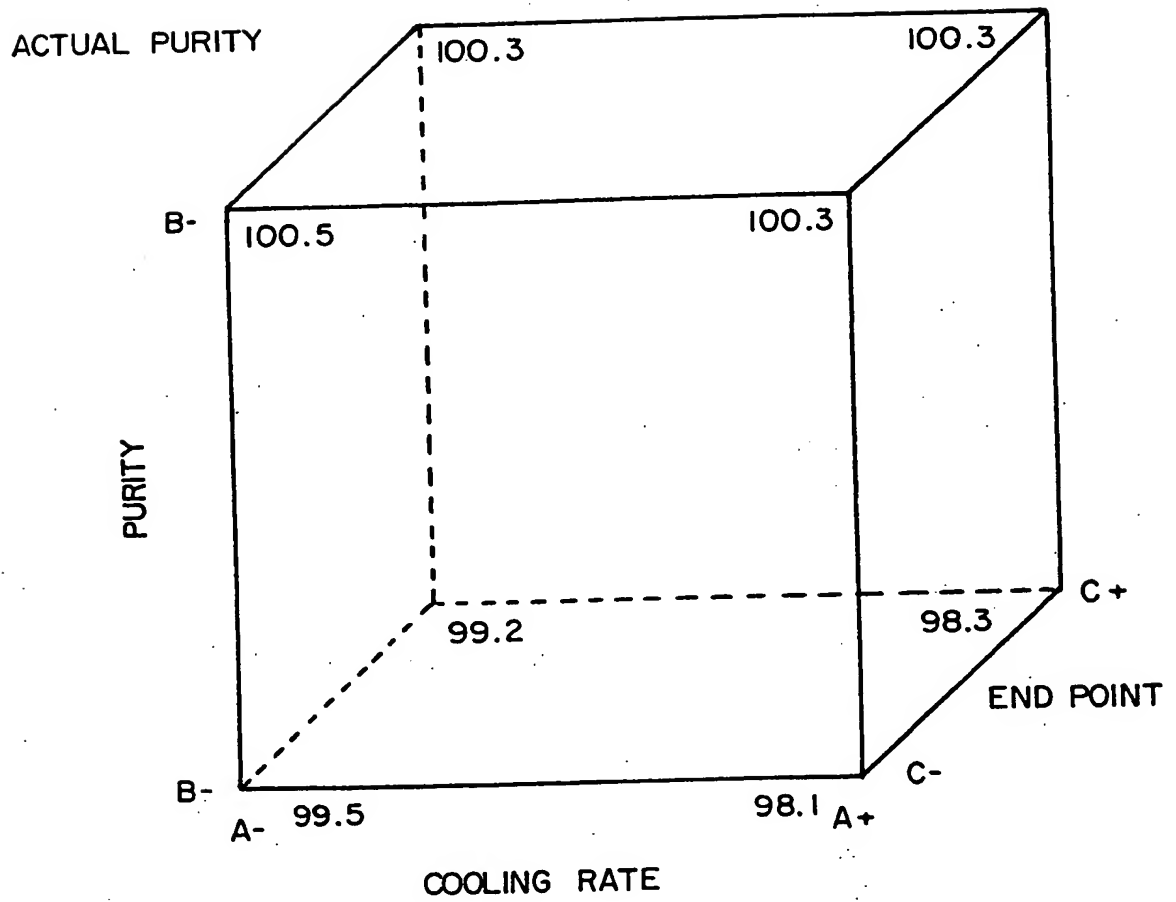


Fig. C-7

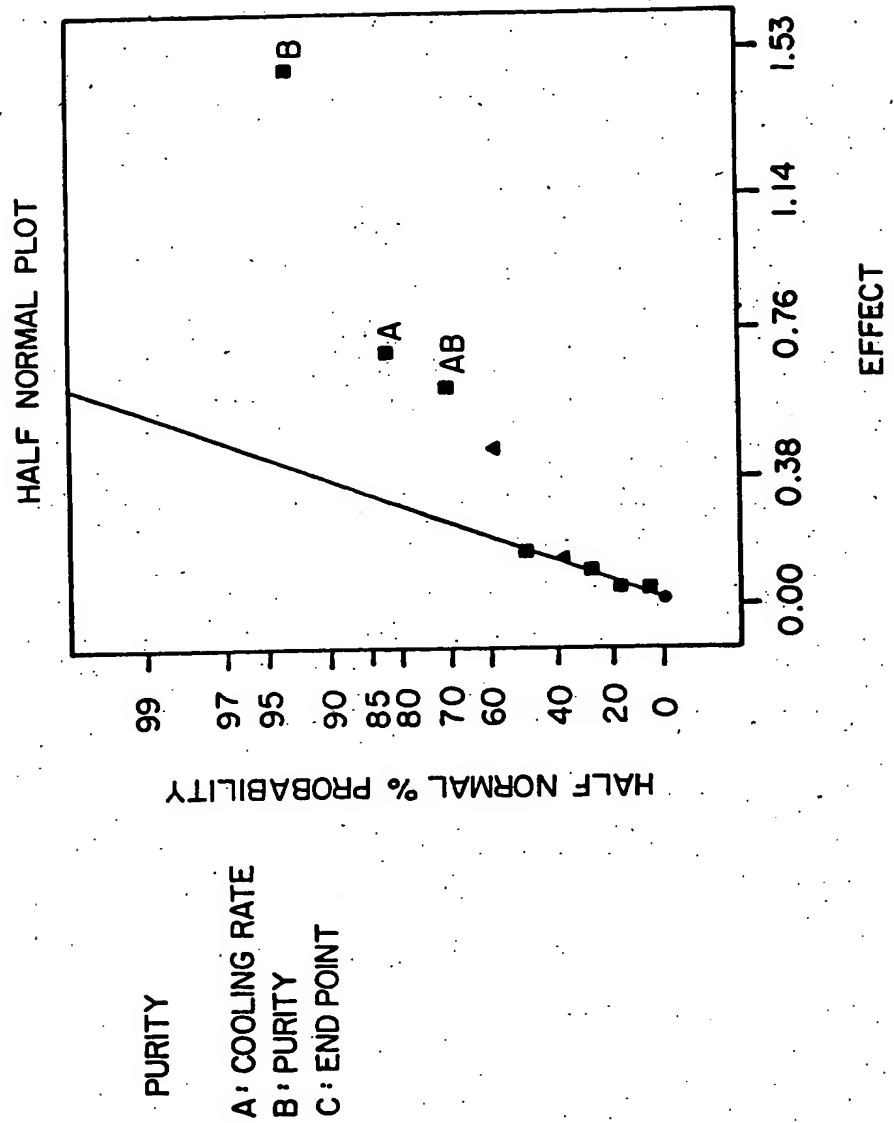


Fig. C-8

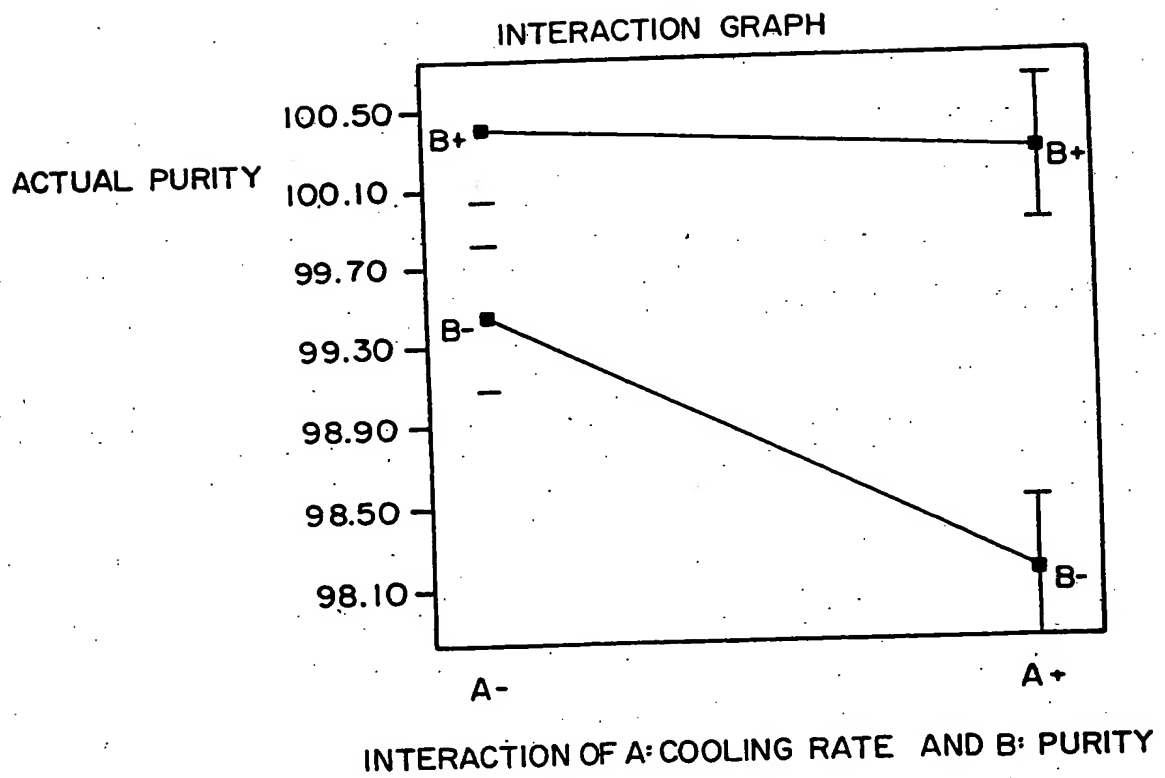
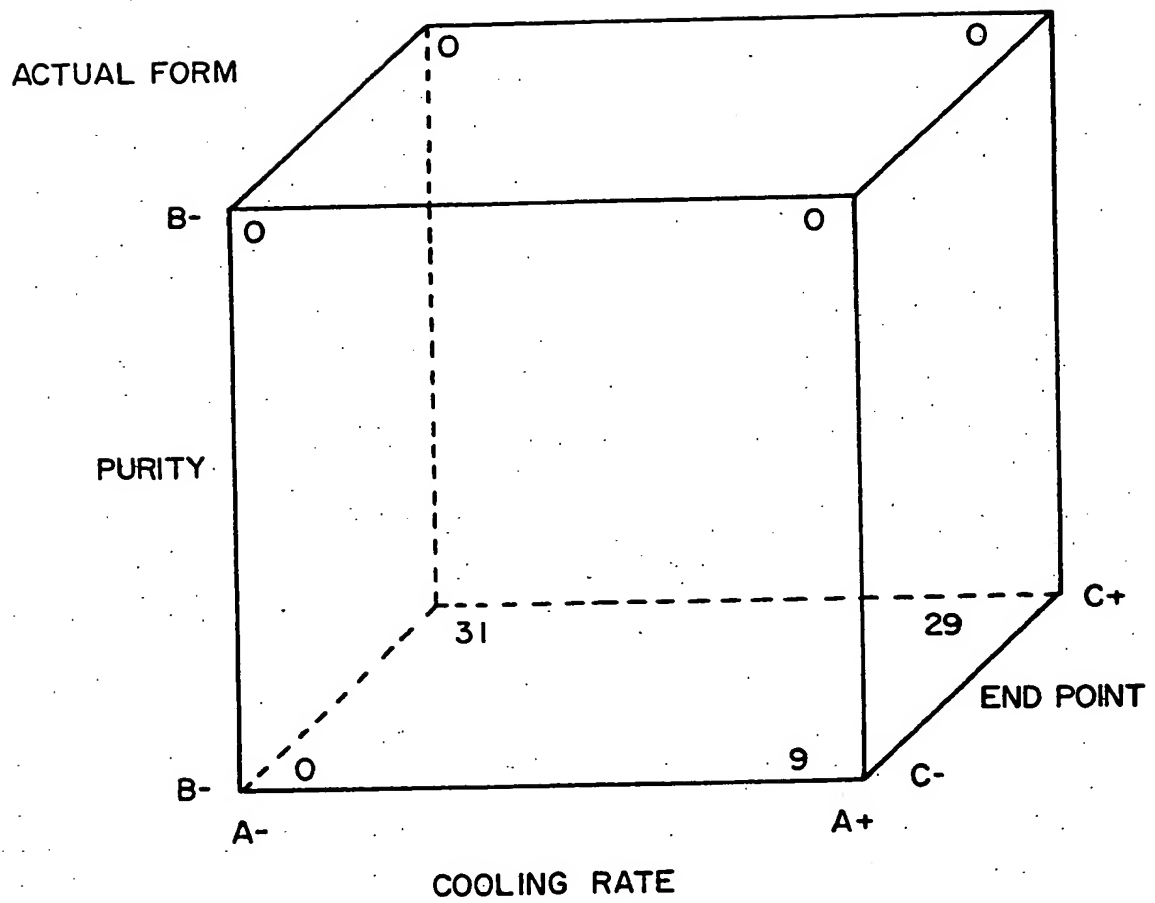


Fig. C-9



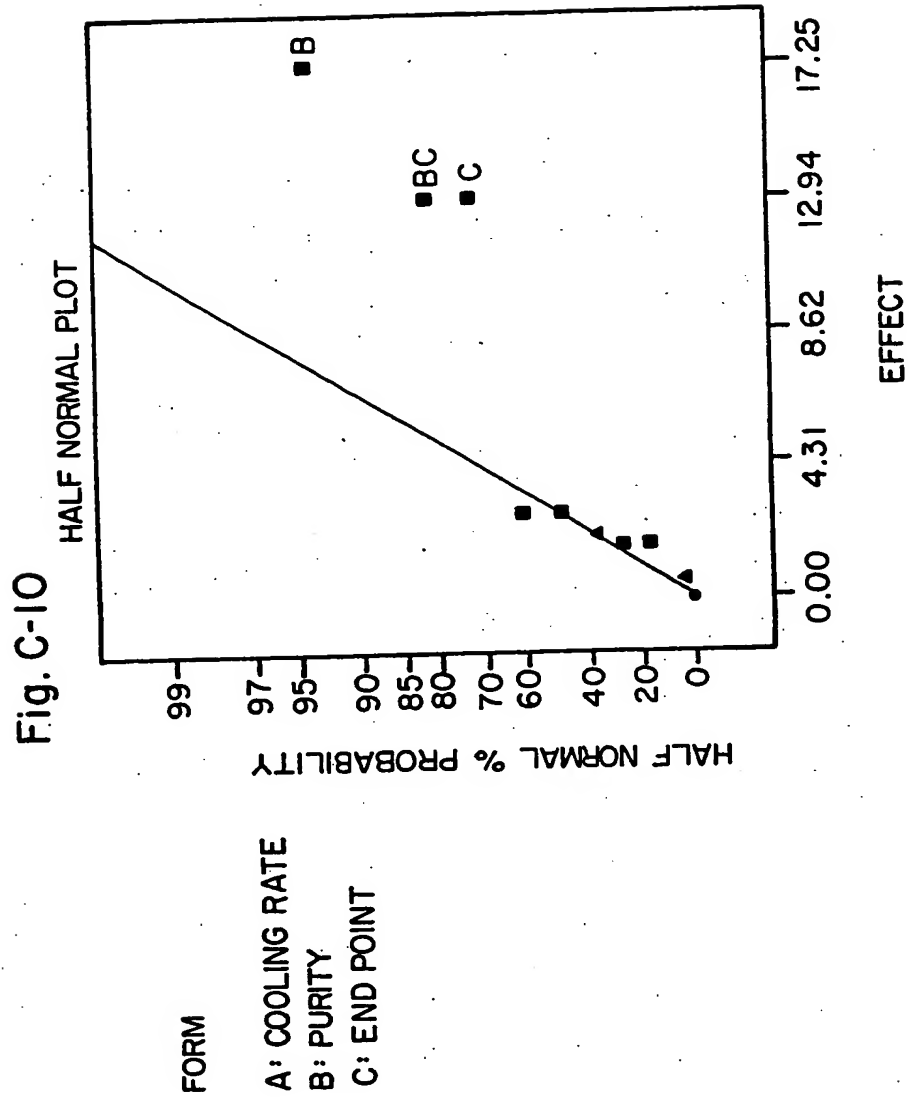
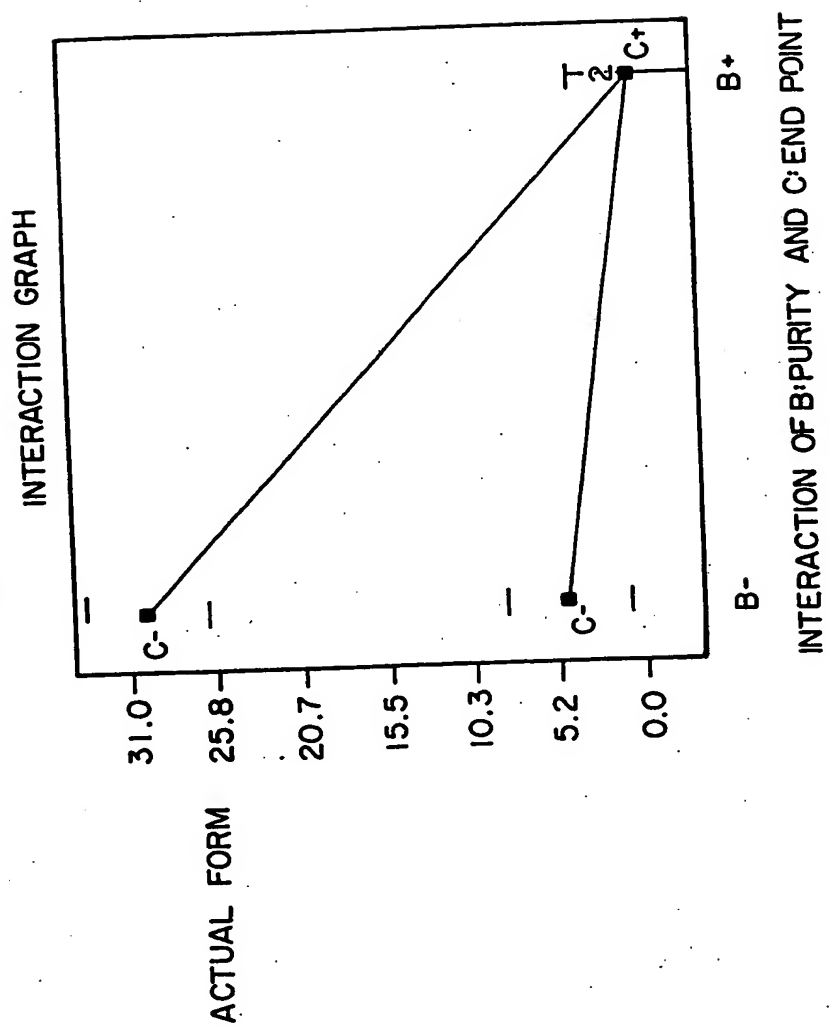


Fig. C-II





65/144

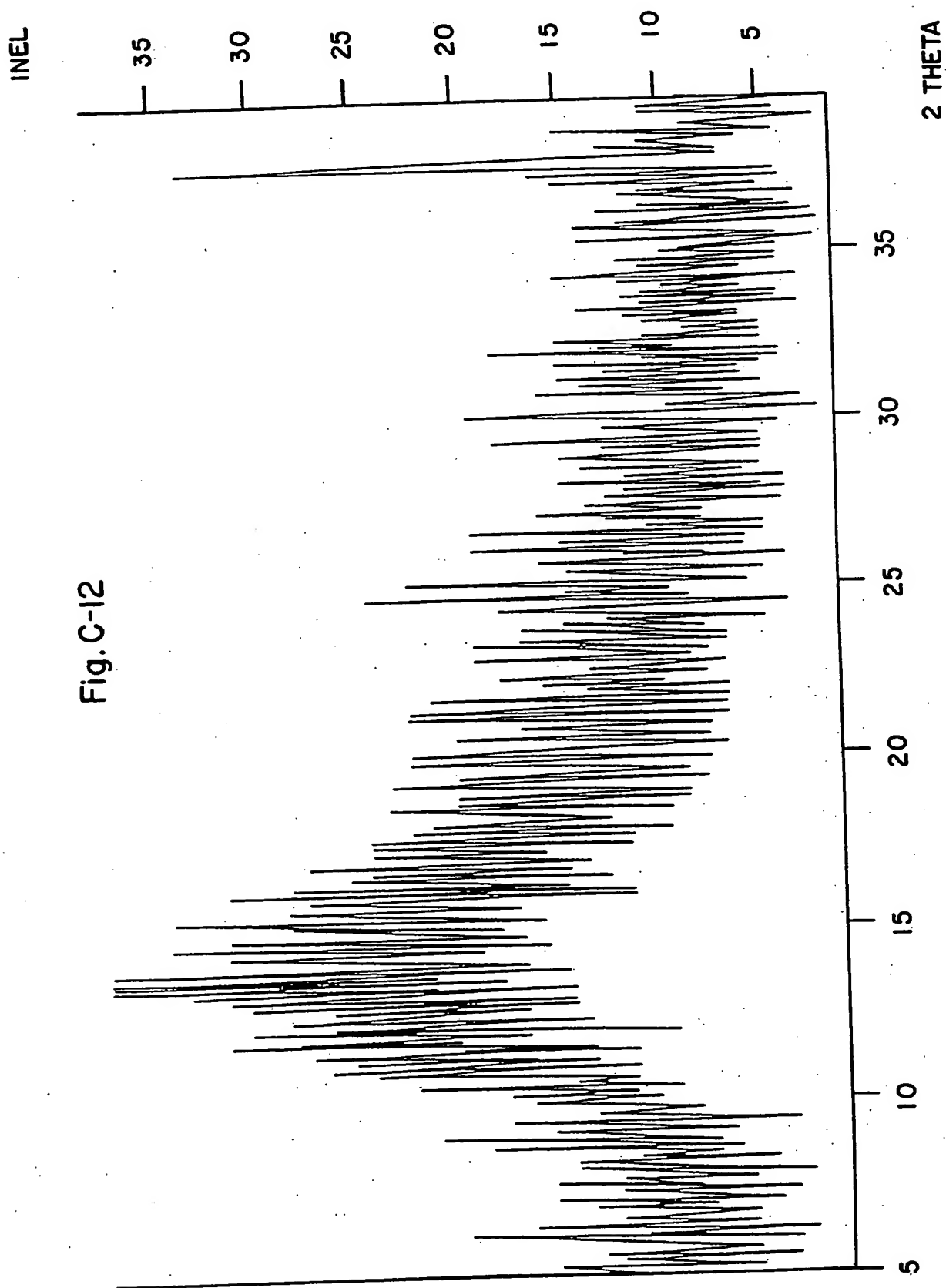


Fig. C-12

INEL

Fig. C-13

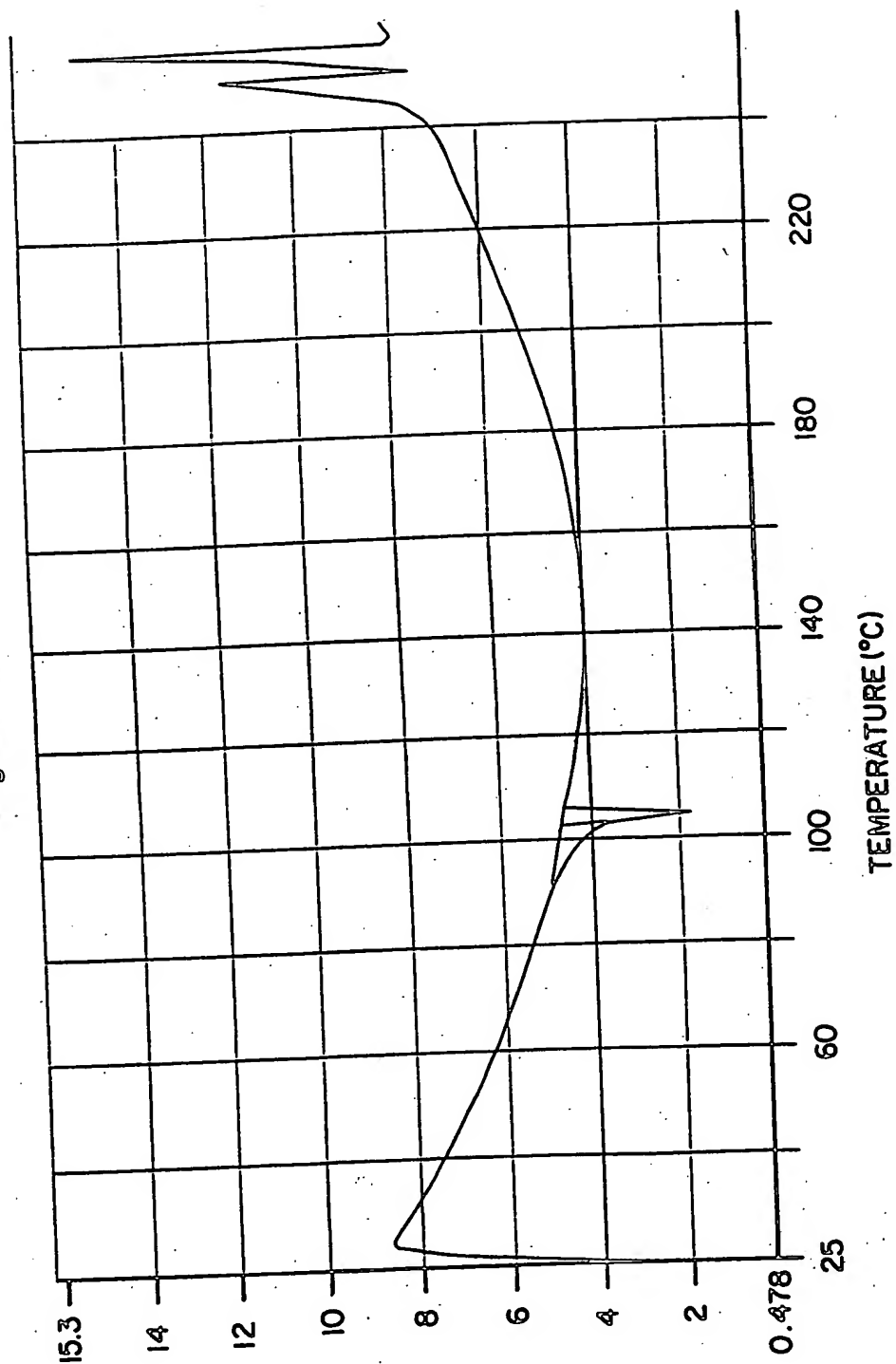
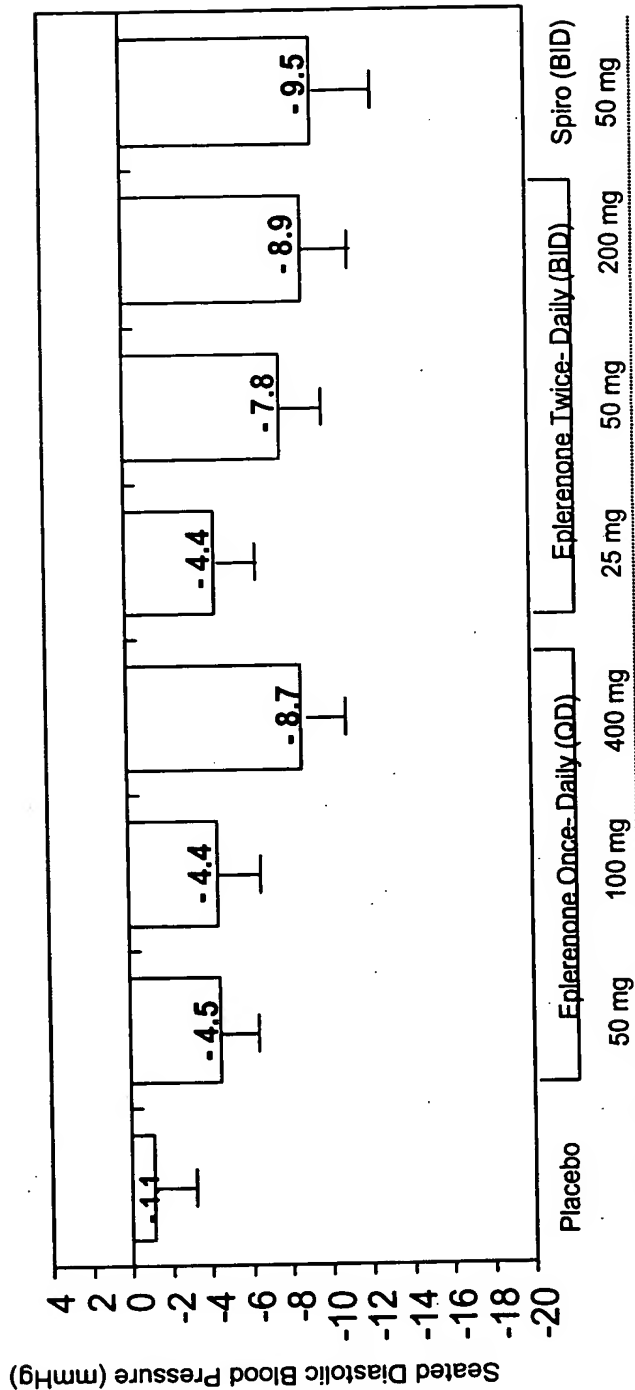


Figure D-1 - Mean Change From Baseline in DBP (N = 409)



N 52

54

48

53

53

47

P-Values vs. Placebo

0.027

0.036

&lt; 0.001

0.031

&lt; 0.001

&lt; 0.001

### P-Values vs. Placebo

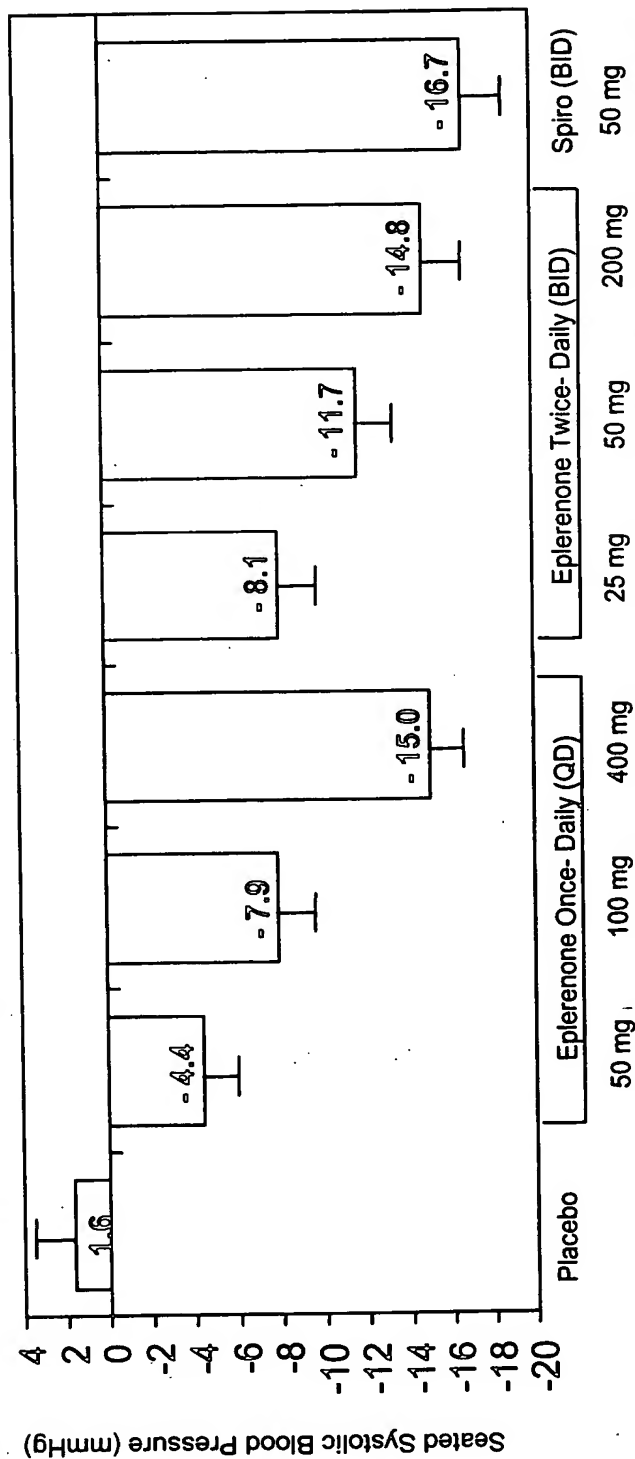


Figure D-3 - Dose Range Factorial Design

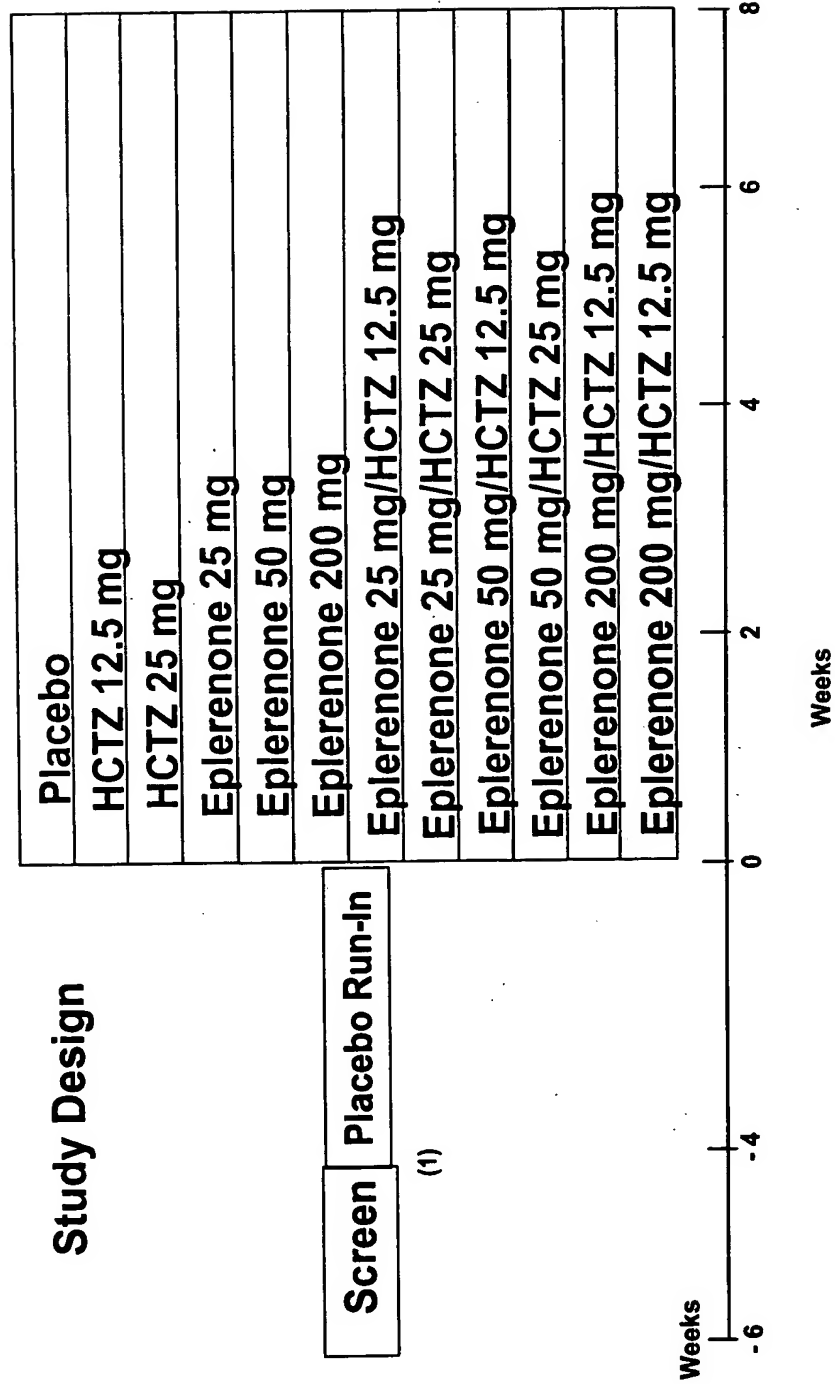
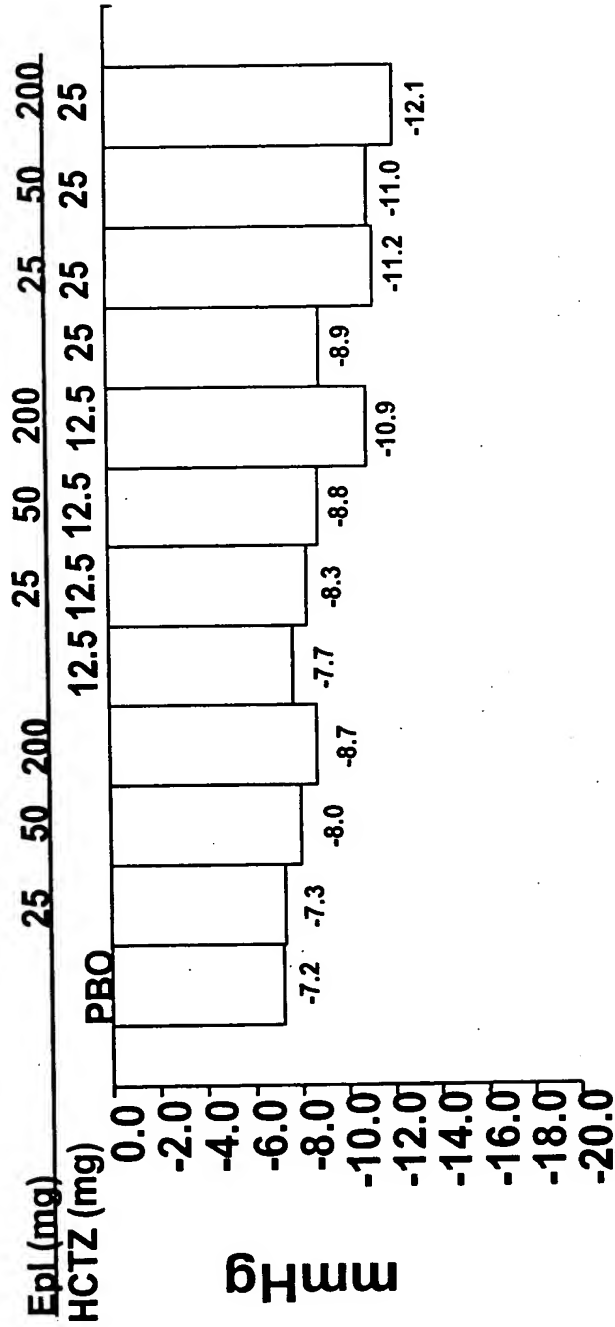


Figure D-4 - Dose-Range Factorial Design - Mean Change in DBP at Final Visit



Figur D-5 - Dose-Range Factorial Design - Mean Change in SBP at Final Visit

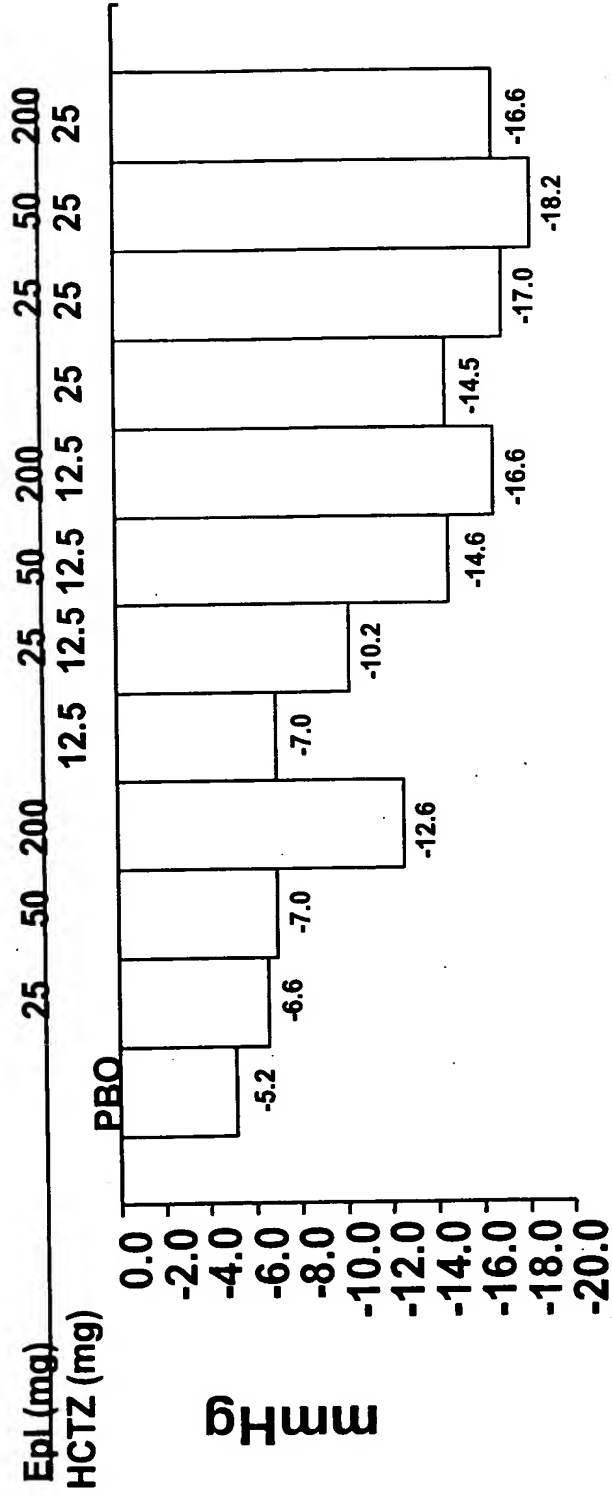
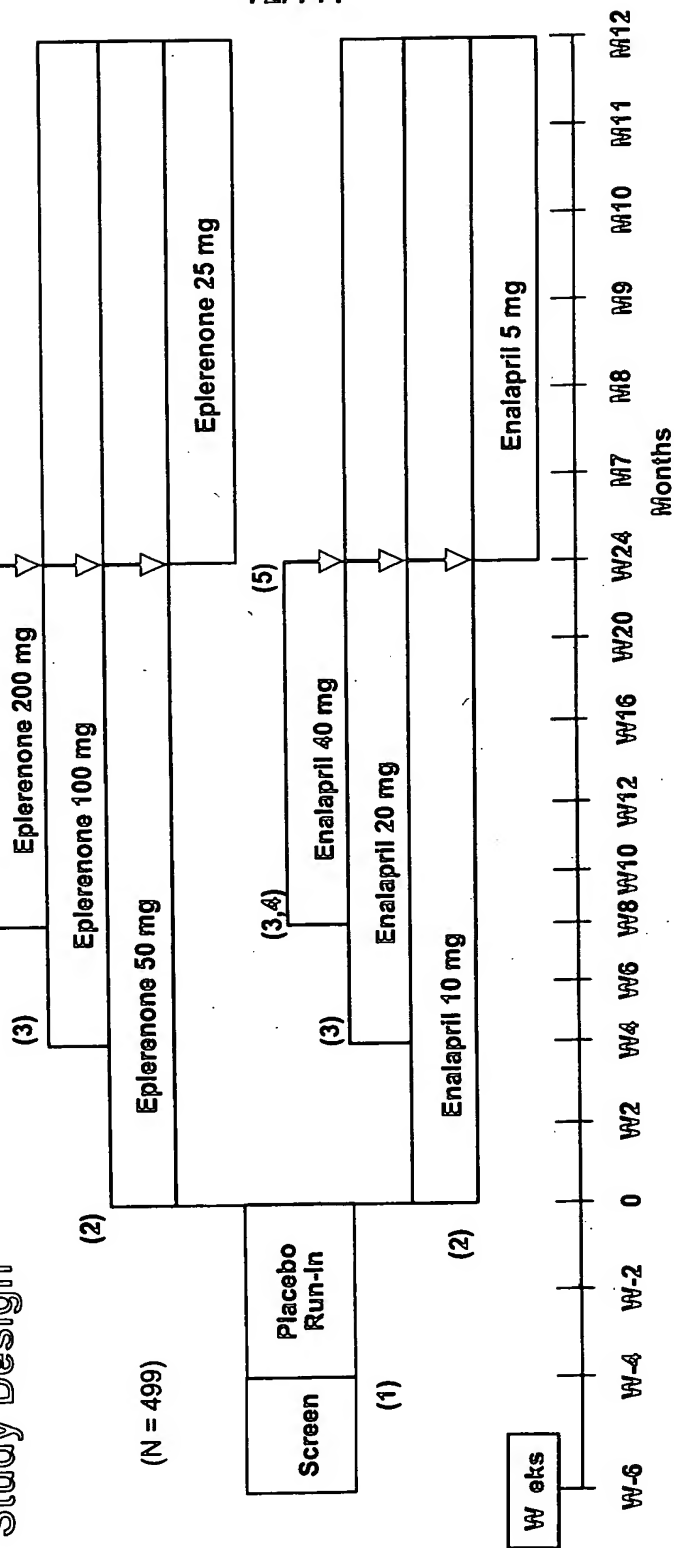
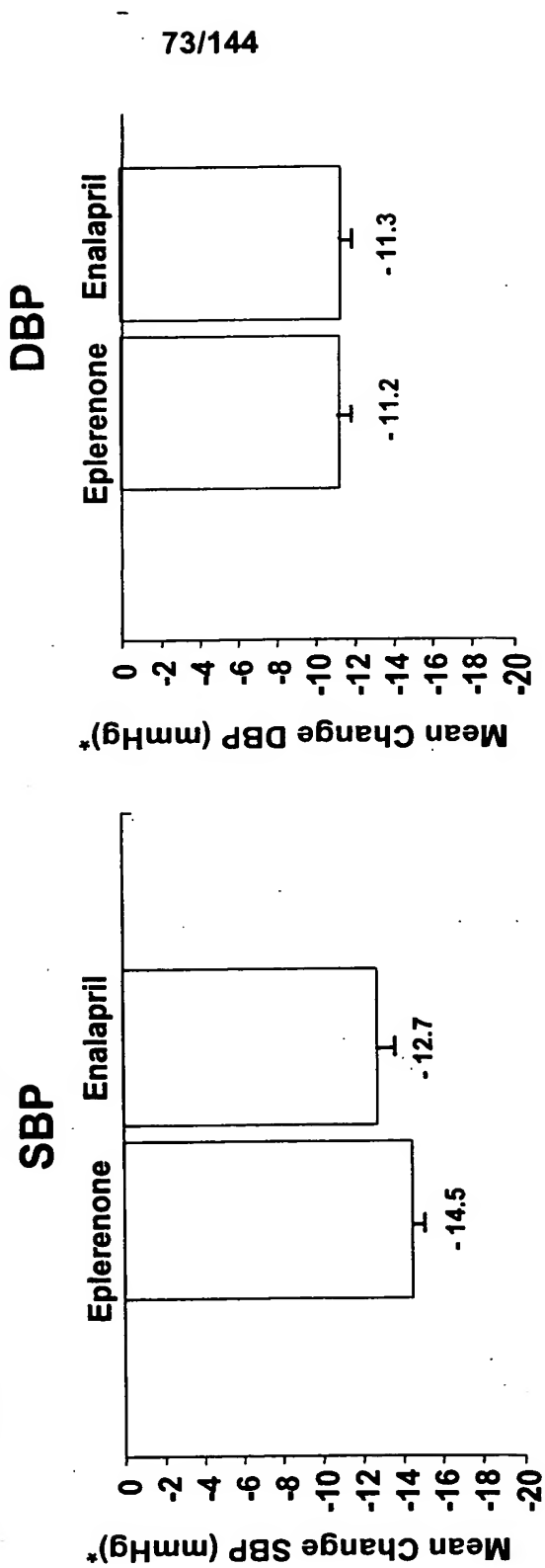


Figure D-6 - Titrated Dose of Eplerenone vs Enalapril  
Study Design

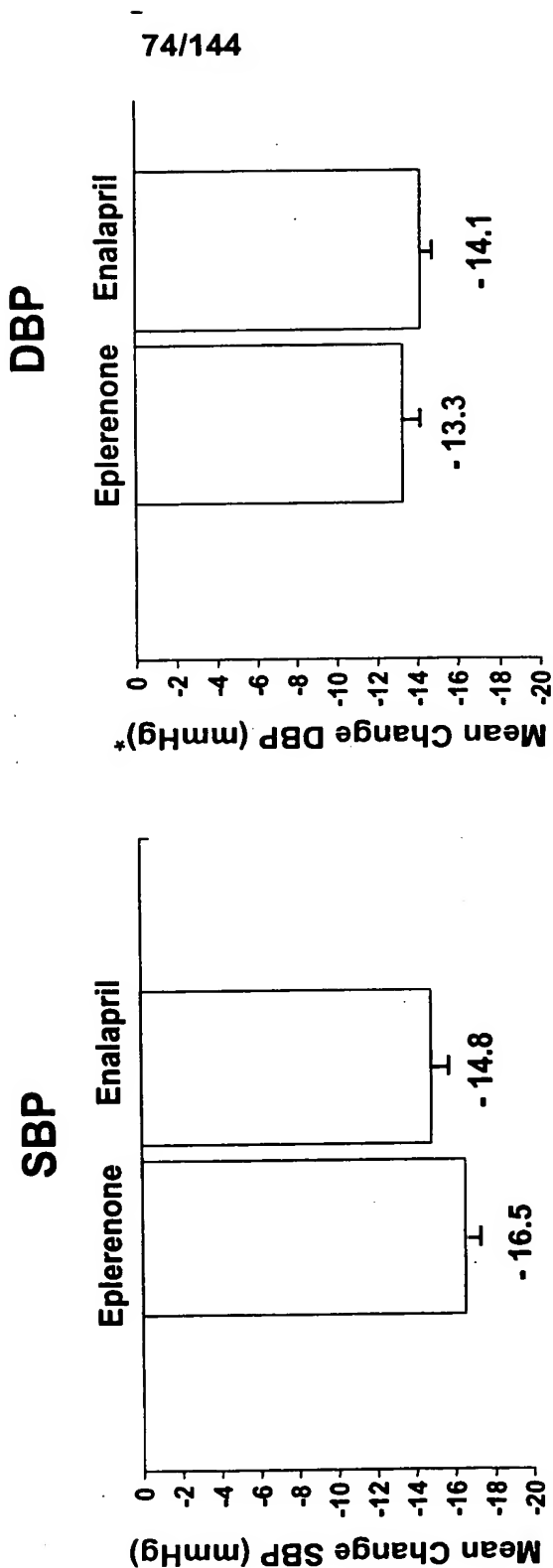




**Figure D-7 - Titrated Dose of Eplerenone vs Enalapril - Mean Change From Baseline in BP (Week 24)**



**Figure D-8 - Titrated Dose of Eplerenone vs Enalapril**  
**Mean Change From Baseline in BP**  
**(Month 12)**

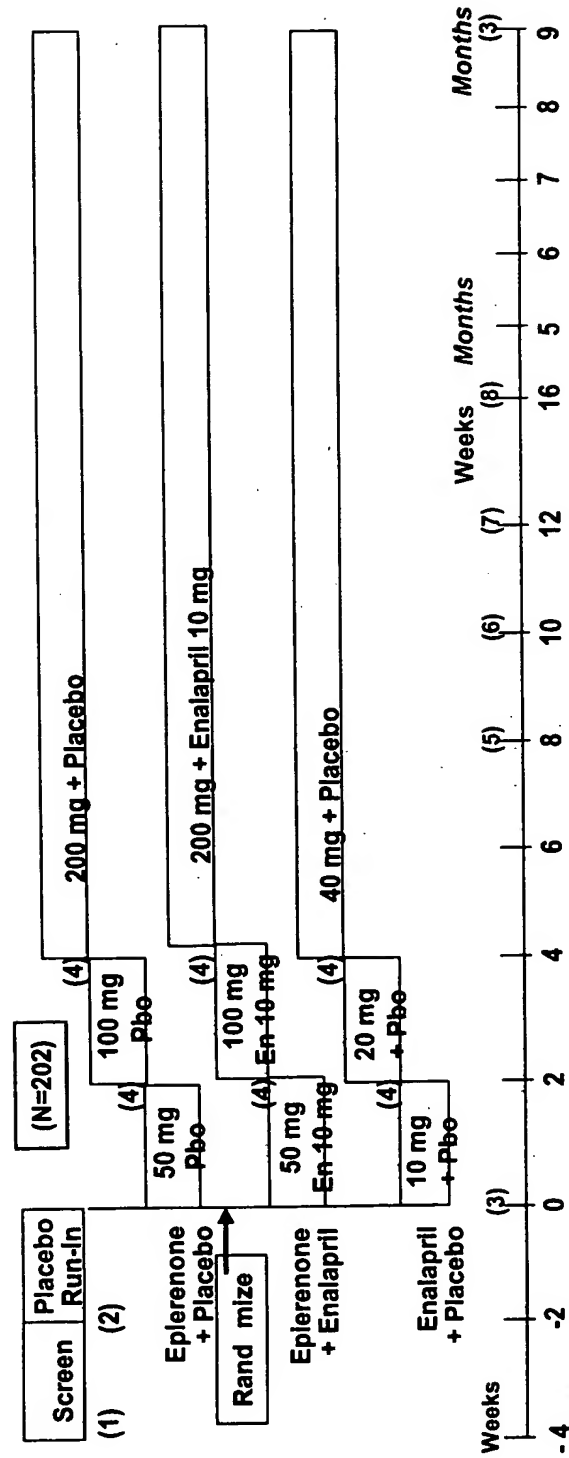


**Figure D-9 - Titrated Dose of Eplerenone vs Enalapril  
Adverse Events of Special Interest**

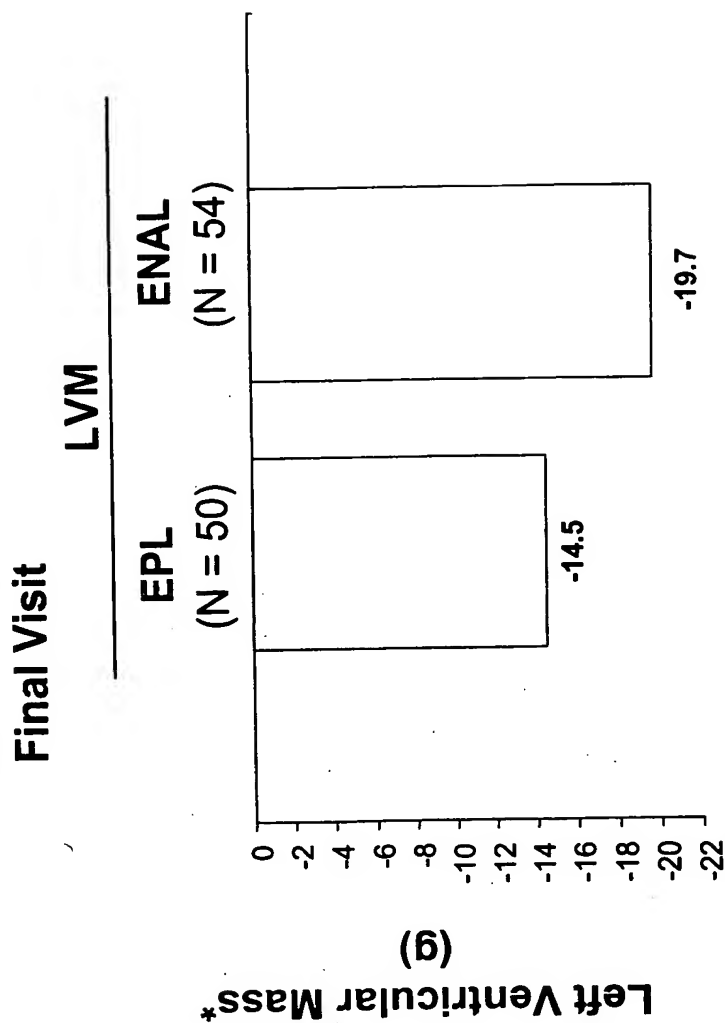
<b><u>AEs ([N(%)])</u></b>	<b><u>Eplerenone (N = 253)</u></b>	<b><u>Enalapril (N = 246)</u></b>
Hyperkalemia	2 (0.8)	2 (0.8)
Hyperuricemia	2 (0.8)	4 (1.6)
Increased Lab Values		
GGT	3 (1.2)	3 (1.2)
SGOT	2 (0.8)	3 (1.2)
SGPT	3 (1.2)	1 (0.4)
BUN	1 (0.4)	1 (0.4)
Impotence*	1 (0.7)	2 (1.6)
Gynecomastia	2 (0.8)	0
Hypotension	3 (1.2)	1 (0.4)
Hypokalemia	0	0
Menstrual Abnormalities**	0	0

\* N = 150 (Eplerenone) and 126 (Enalapril) Male \*\* N = 103 (Eplerenone) and 120 (Enalapril) Female

**Figure D-10 - Eplerenone vs. Enalapril vs. Combination with (LVH)  
- Study Design**



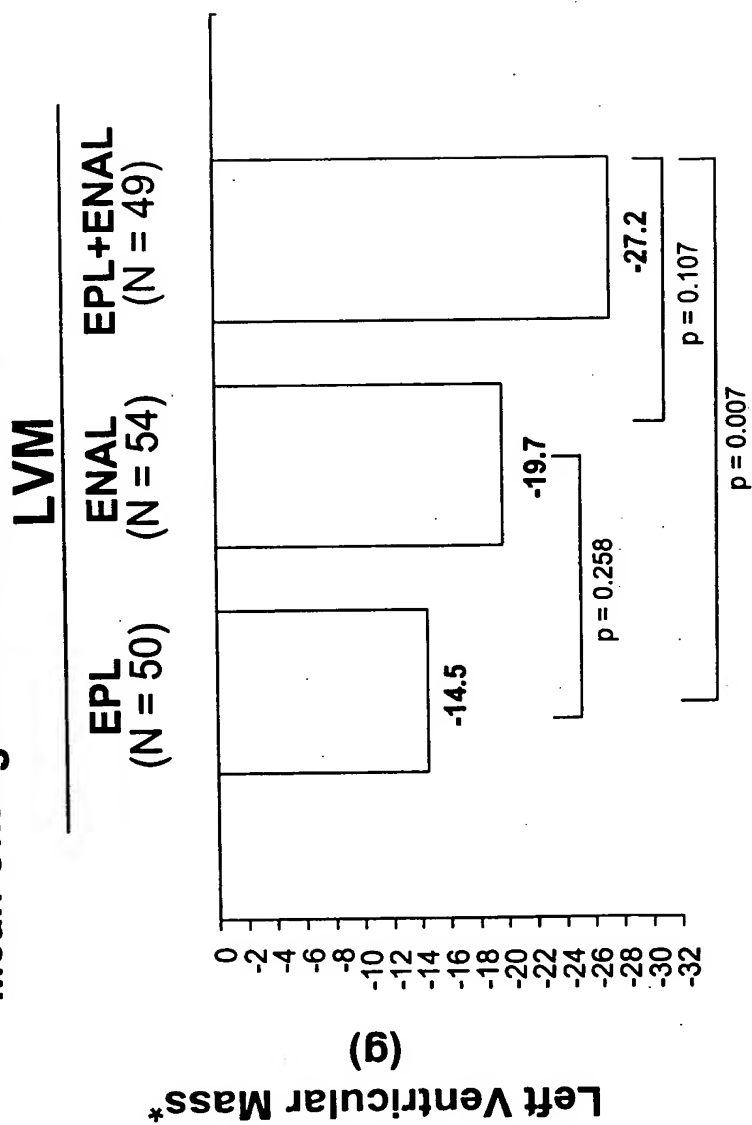
**Figure D-11 - Eplerenone vs. Enalapril vs. Combination with (LVH)  
Mean Change from Baseline LVM:**



Non-inferiority is established if the lower confidence limit for LVM > -15 g

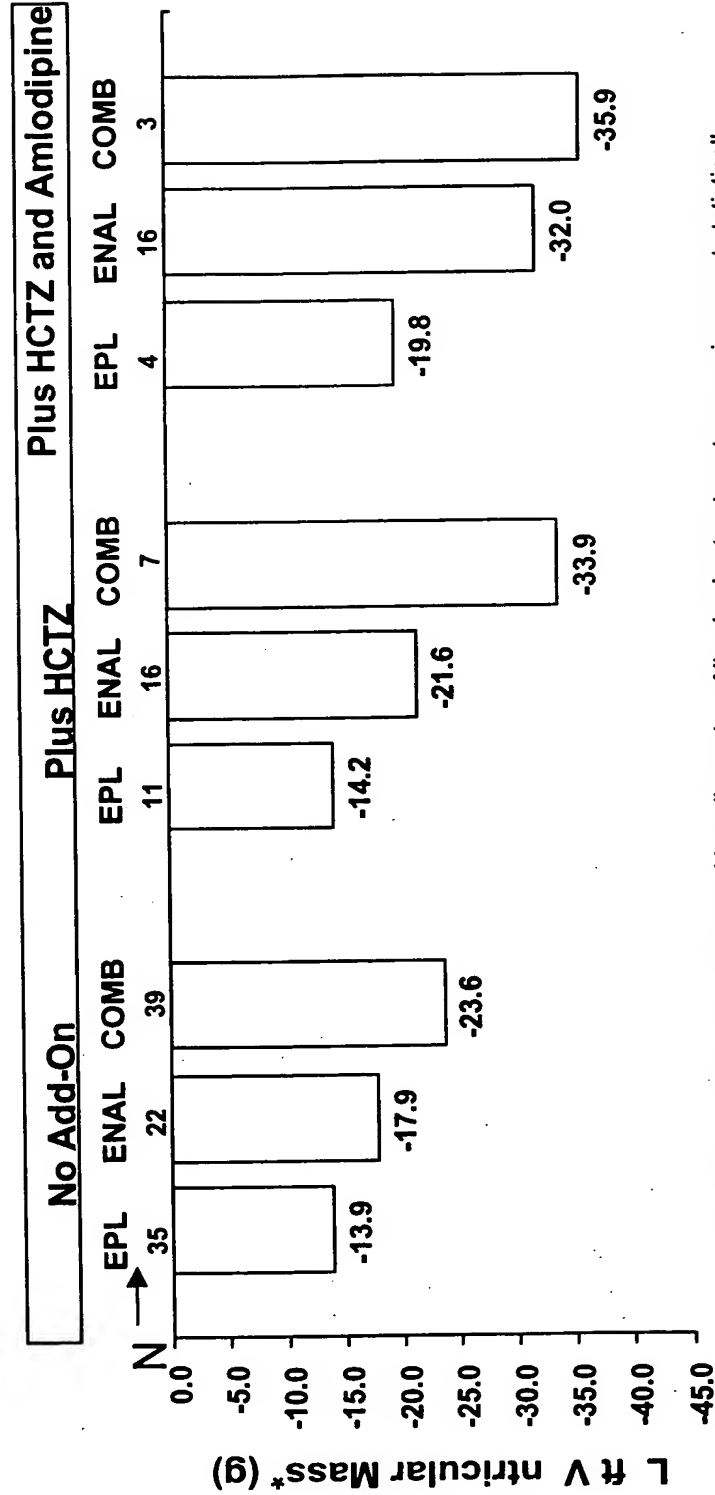
\* Adjusted to treatment, center, and baseline value

**Figure D-12 - Eplerenone vs. Enalapril vs. Combination with (LVH)**  
**Mean Change from Baseline LVM: Final Visit**



\* Adjusted to treatment, center, and baseline value. All reductions statistically significant vs. Baseline

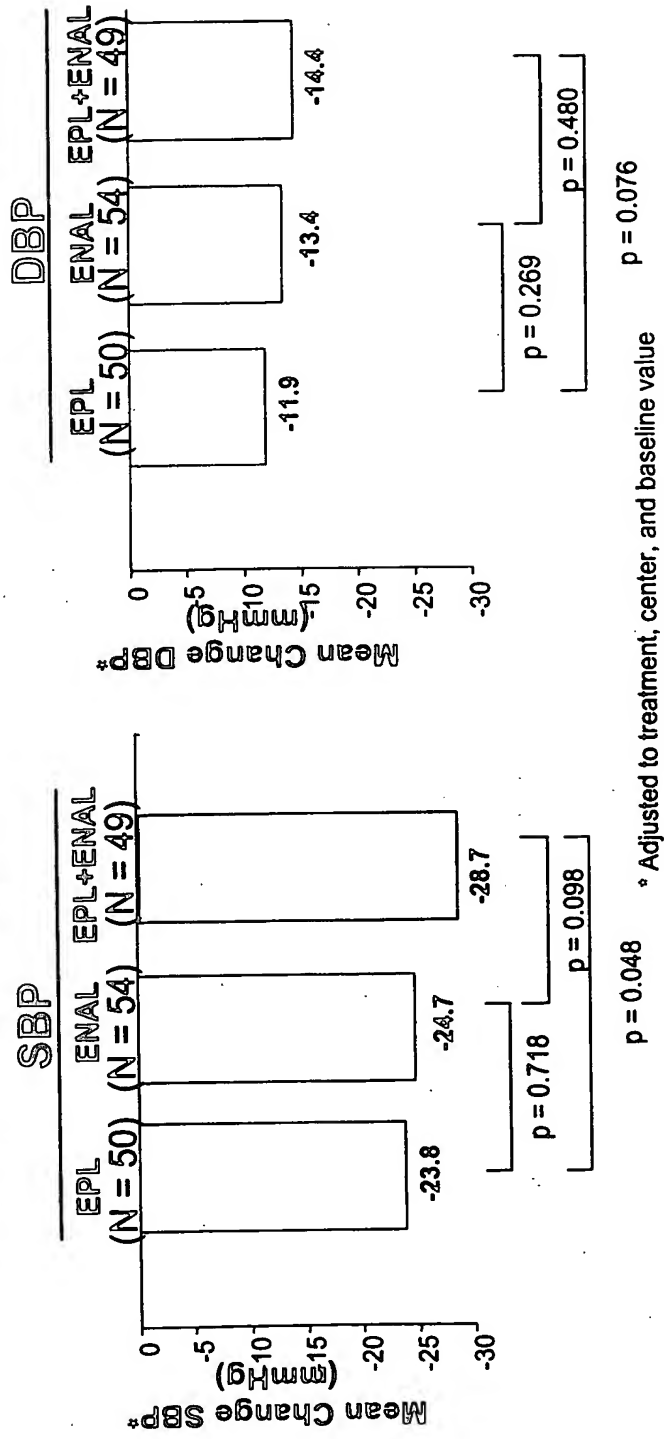
**Figure D-13 - Eplerenone vs. Enalapril vs. Combination with (LVH)  
Mean Change from Baseline in LVM**



\* Adjusted to treatment, center, and baseline value. All pair wise treatment comparisons not statistically significant

Figure D-14 - Eplerenone vs. Enalapril vs. Combination with (LVH)

Mean Change from Baseline BP: LVH Patients Final Visit



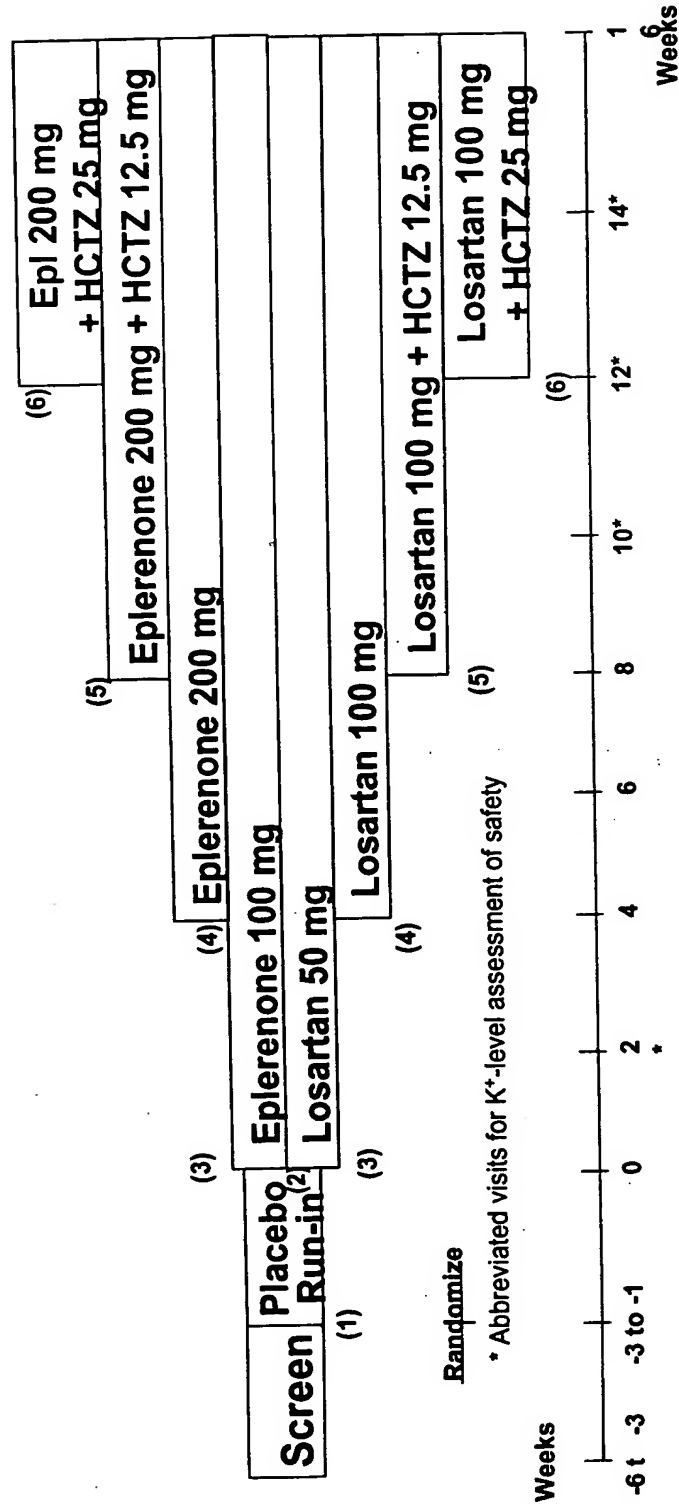


**Figure D-15 - Eplerenone vs. Enalapril vs. Combination with (LVH)**  
**Events of Special Interest**

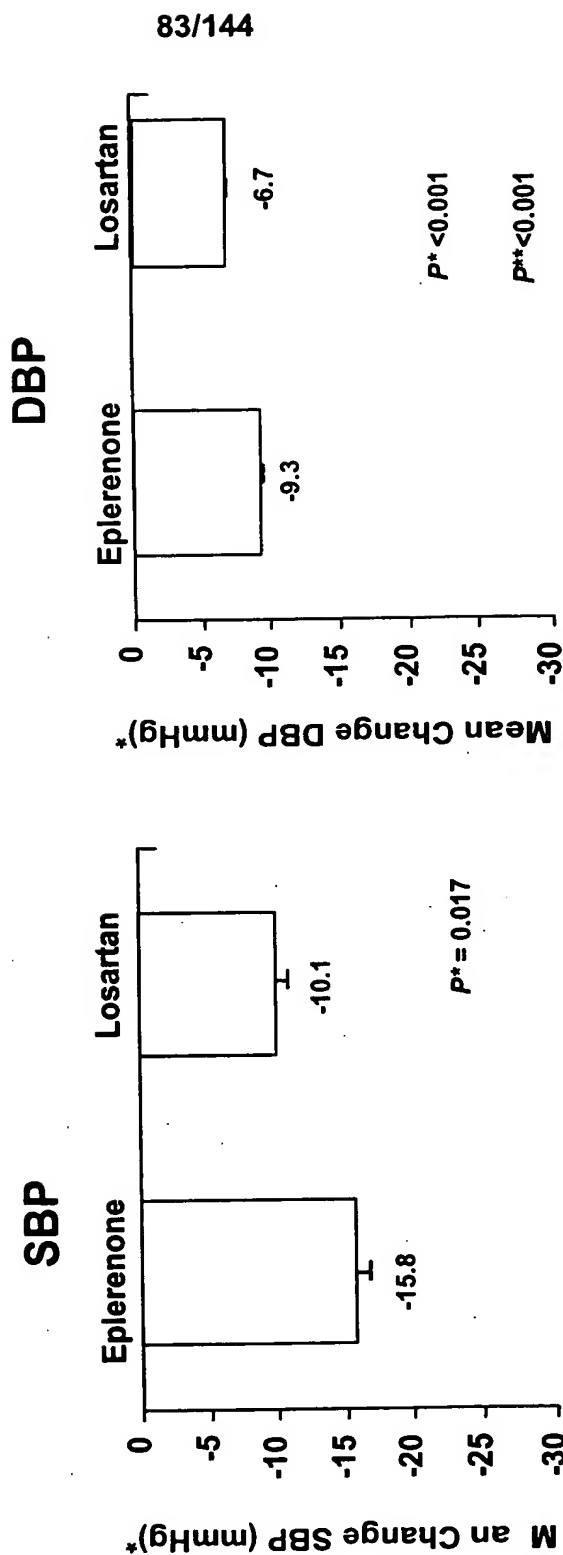
<b>AEs [N(%)]</b>	<b>EPL (N = 64)</b>	<b>ENA (N = 71)</b>	<b>EPL+ENA (N = 67)</b>
Hyperkalemia	4 (6.3)	1 (1.4)	1 (1.5)
Hyperuricemia	1 (1.6)	2 (2.8)	0 (0.0)
Increased Lab Values			
GGT	1 (1.6)	3 (4.2)	1 (1.5)
SGOT	2 (3.1)	2 (2.8)	2 (3.0)
SGPT	2 (3.1)	2 (2.8)	0 (0.0)
BUN	1 (1.6)	0 (0.0)	0 (0.0)
Impotence*	0 (0.0)	3 (6.8)	1 (2.2)
Gynecomastia*	1 (2.5)	0 (0.0)	1 (2.2)
Hypotension	1 (1.6)	2 (2.8)	3 (4.5)
Hypokalemia	0 (0.0)	2 (2.8)	0 (0.0)
Menstrual Abnormalities	0 (0.0)	0 (0.0)	0 (0.0)
Brust Pain, Female	0 (0.0)	0 (0.0)	0 (0.0)
Cough	2 (3.1)	10 (14.1)	6 (9.0)

\* N = 40 (EPL); 44 (ENAL); 45 (EPL+ENAL)

**Figure D-16 - Low Renin Hypertension  
Study Design**

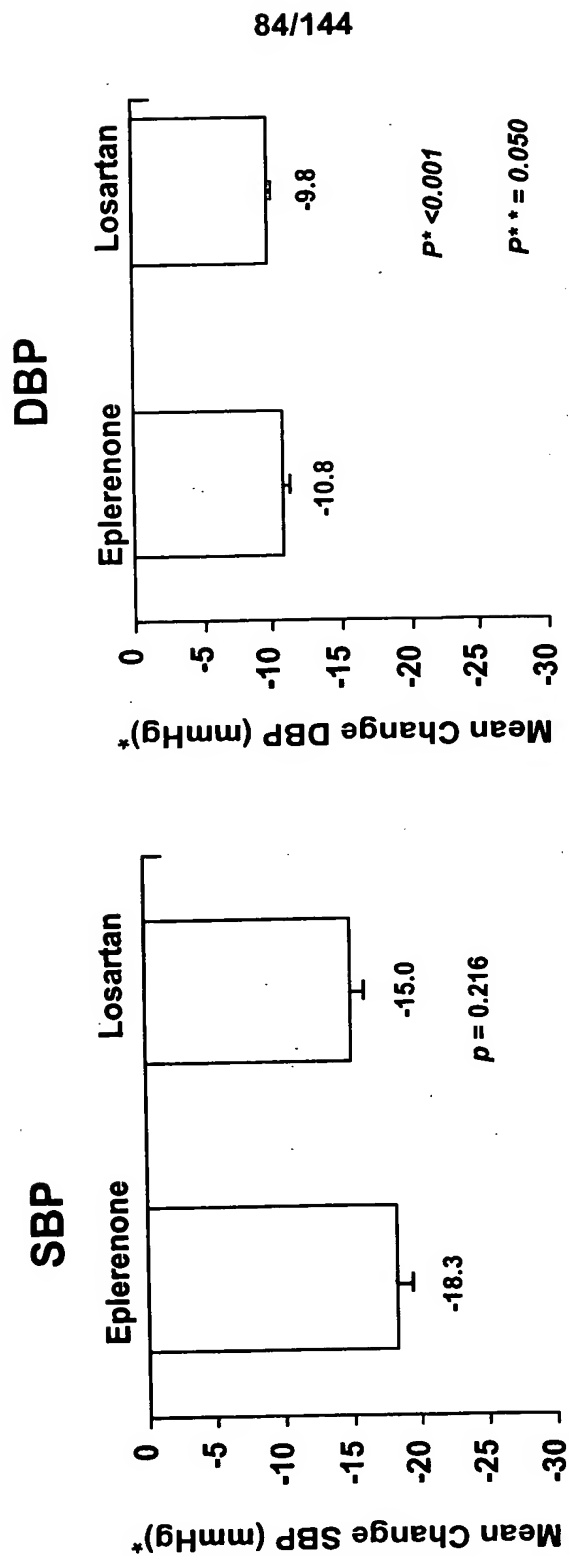


**Figure D-17 - Low Renin Hypertension  
Mean Change From Baseline in BP  
Week 8 (Monotherapy Endpoint)**



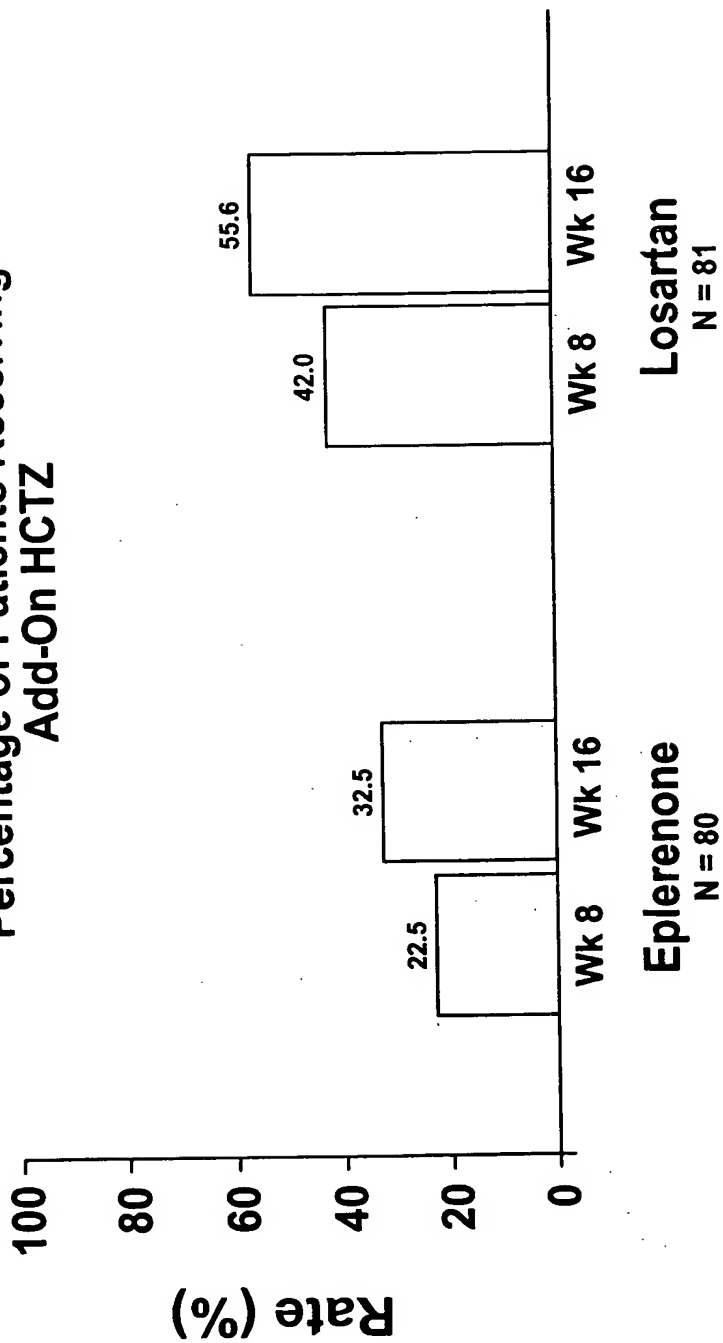
\* Non-Inferiority test    \*\* Two sided test

**Figure D-18 - Low Renin Hypertension**  
**Mean Change From Baseline in BP**  
**Week 16 (Final Visit)**



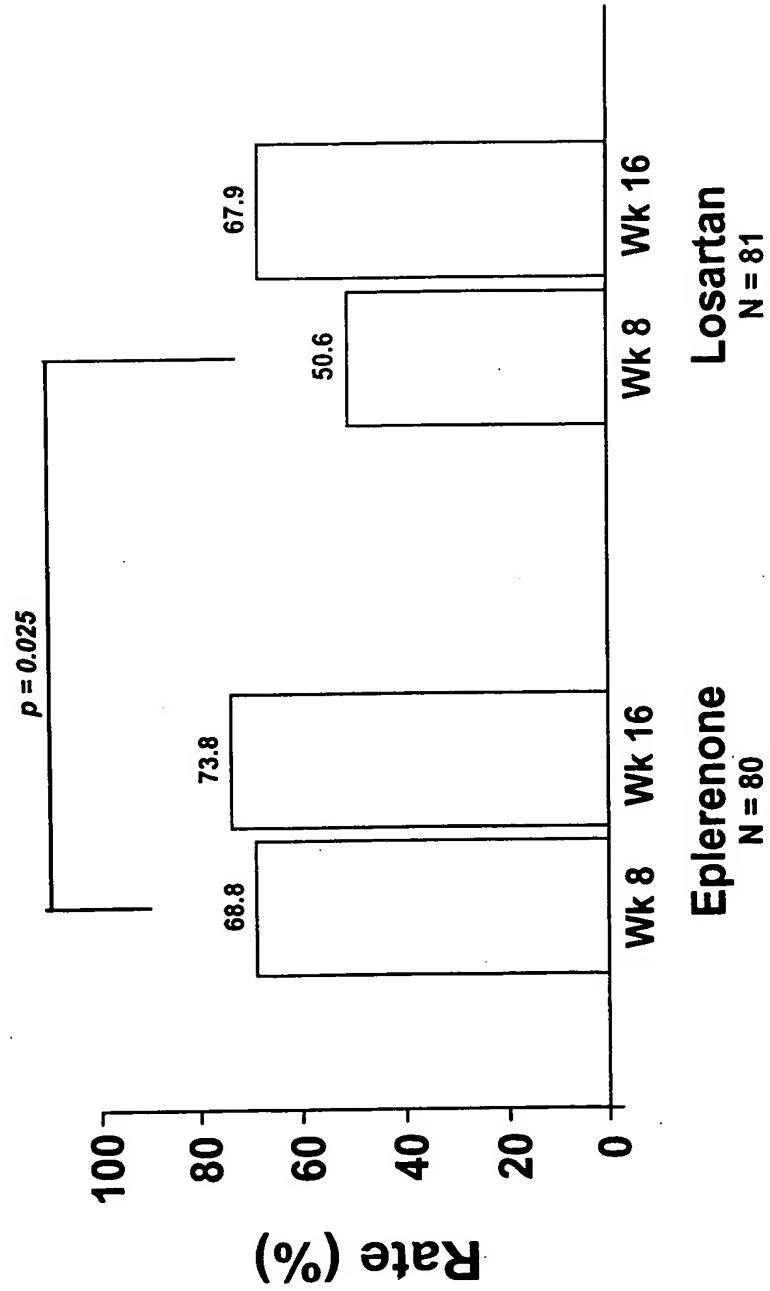
\* N n-Inferiority test    \*\* Two sided test

**Figure D-19 - Low Renin Hypertension  
Percentage of Patients Receiving  
Add-On HCTZ**



L g-rank test:  $p = 0.002$

**Figure D-20 - Low Renin Hypertension - Responder Rates**



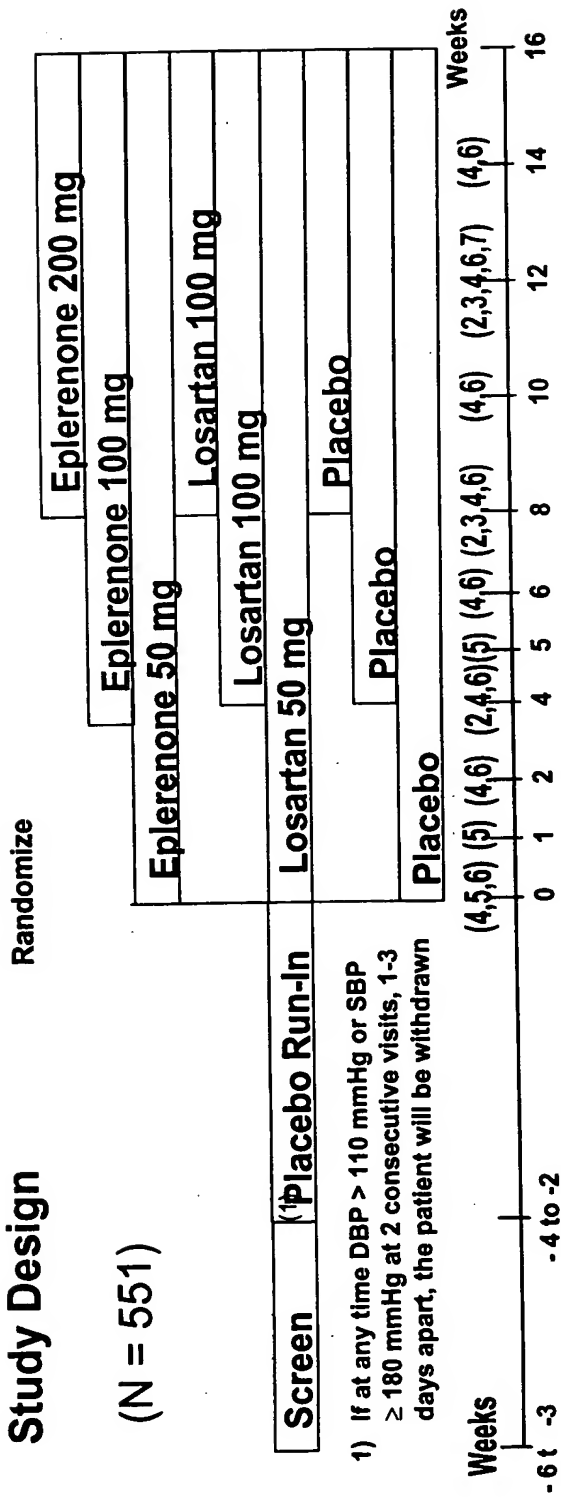
Responder defined as: seDBP < 90 mmHg or seDBP  $\geq$  10 mmHg reduction from baseline

Figure D-21 - Low Renin Hypertension - Adverse Events of Special Interest

<u>Adverse Events N (%)</u>	<u>Eplerenone (N = 86)</u>	<u>Losartan (N = 82)</u>
Gynecomastia*	2 (5.0)	0 (0.0)
Menstrual Disorder	0 (0.0)	1 (2.8)
Hyperkalemia	0 (0.0)	0 (0.0)
Hyperuricemia	2 (2.3)	3 (3.7)
Impotence*	1 (2.5)	1 (2.2)
Increased Lab Values		
GGT	2 (2.3)	1 (1.2)
SGOT	2 (2.3)	1 (1.2)
SGPT	2 (2.3)	1 (1.2)
BUN	0 (0.0)	1 (1.2)
Hypotension	0 (0.0)	0 (0.0)

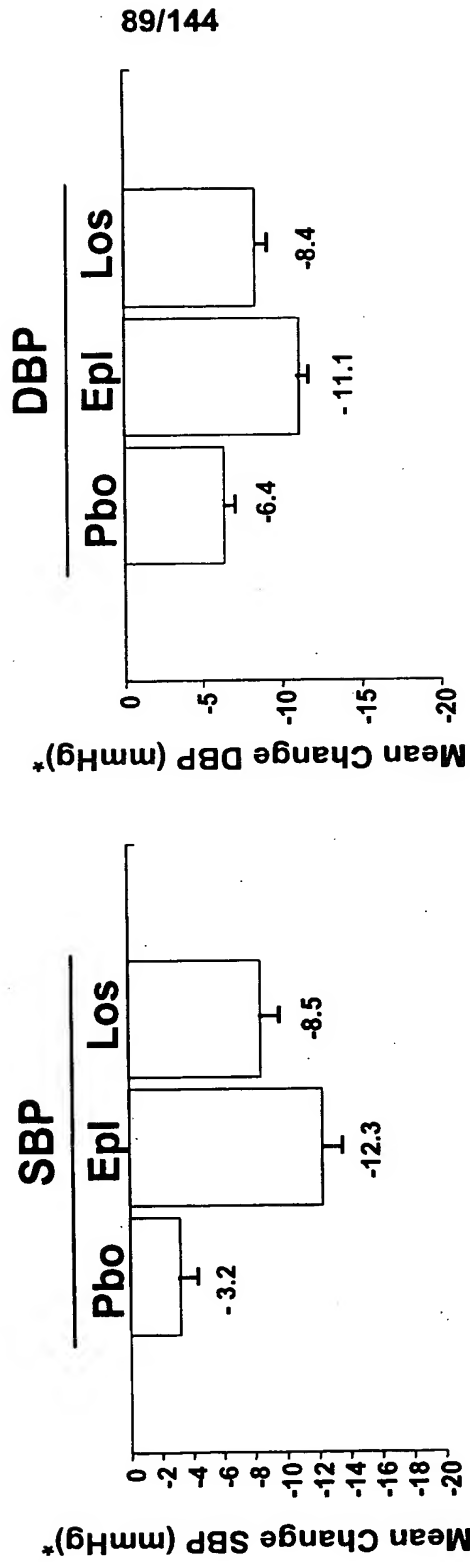
\* Eplerenone N = 40; Losartan N = 46

### Figure D-22 - Comparison in Black and White Populations





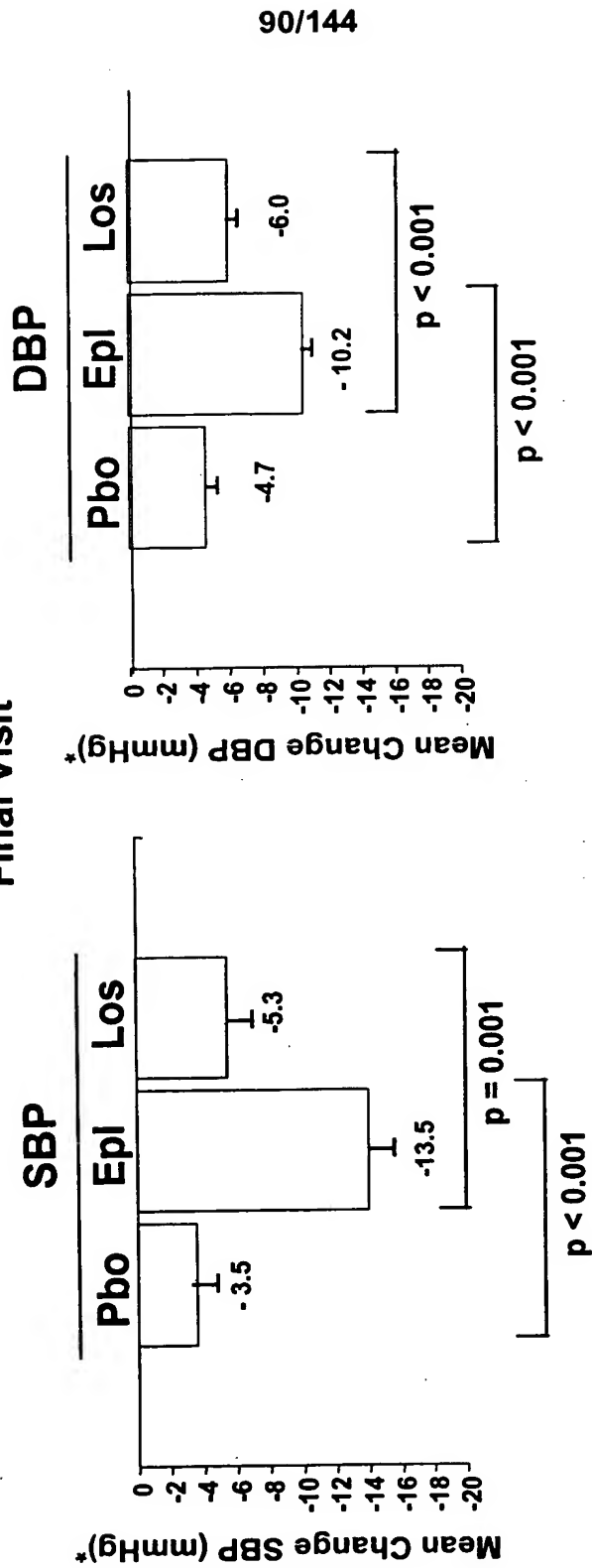
**Figure D-23 - Comparison in Black and White Populations**  
**Mean Change From Baseline: Whites**  
**Final Visit**



\* Adjusted to treatment, center, and baseline value

**Figure D-24 - Comparison in Black and White Populations**

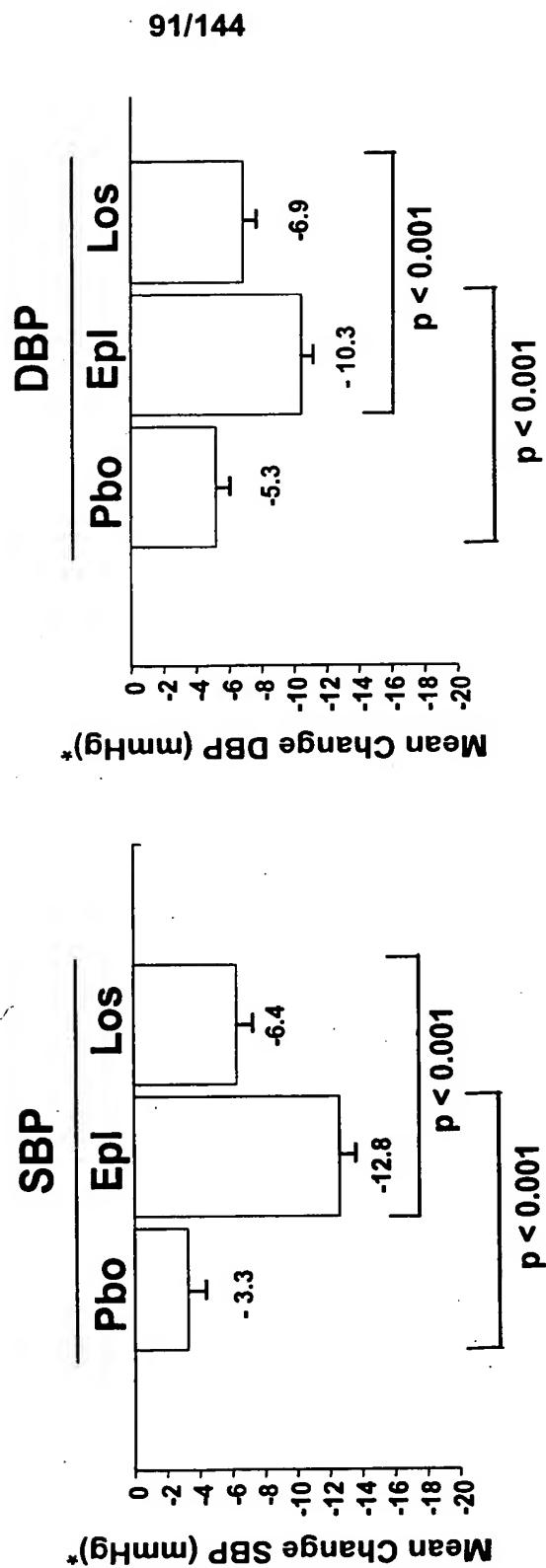
**Mean Change From Baseline: Blacks**  
**Final Visit**



\* Adjusted to treatment, center, and baseline value

**Figure D-25 - Comparison in Black and White Populations**

**Mean Change From Baseline: All Patients Final Visit**



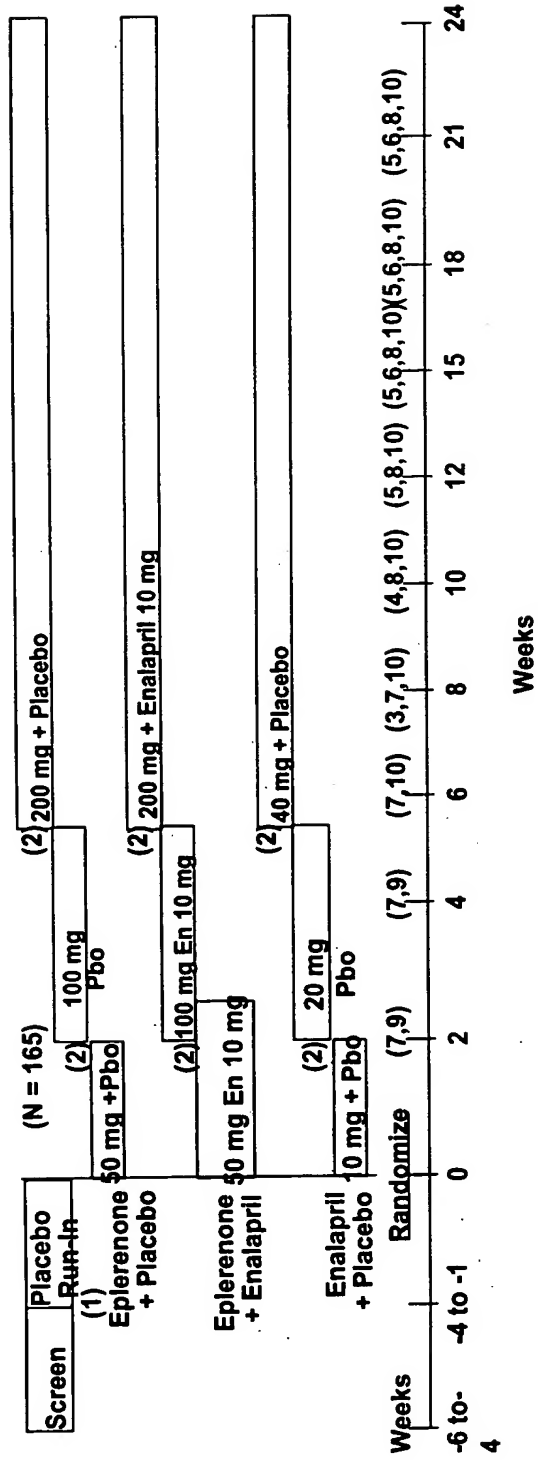
\* Adjusted to treatment, center, and baseline value

**Figure D-26 - Comparison in Black and White Populations  
Adverse Events of Special Interest**

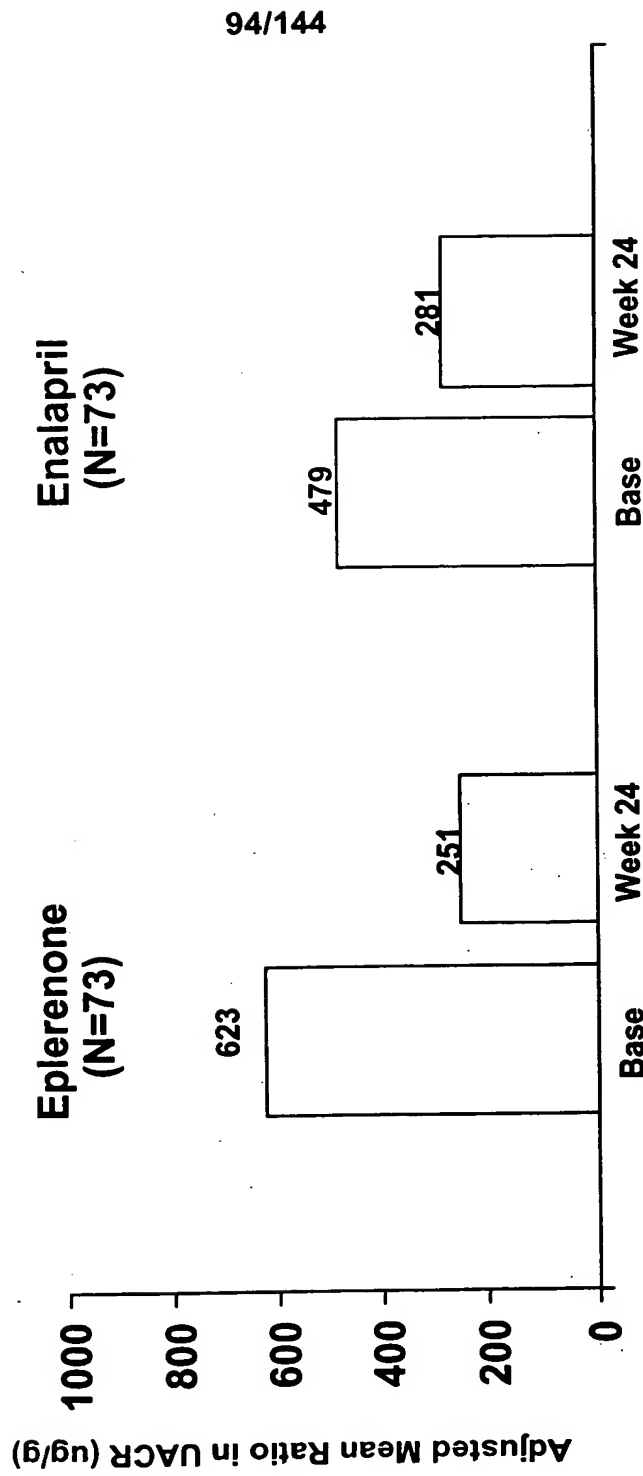
<b>AEs (N(%))</b>	<b>All Patients</b>		
	<b>Pbo (N = 181)</b>	<b>Epl (N = 182)</b>	<b>Los (N = 188)</b>
Hyperkalemia	1 (0.6)	1 (0.5)	0
Hyperuricemia	0	0	0
Increased Lab Values			
GGT	0	0	2 (1.1)
SGOT	1 (0.6)	0	1 (0.5)
SGPT	2 (1.1)	0	1 (0.5)
BUN	0	0	0
Impotence*	1 (1.2)	0	1 (1.2)
Gyn comastia	0	0	0
Hypotension	0	0	0
Hypokalemia	1 (0.6)	0	1 (0.5)
Menstrual Abnormalities**	0	1 (0.9)	2 (1.1)

**N = 84 (Pbo); 65 (Epl); 83 (Los)      \*\*N = 97 (Pbo); 117 (Epl); 105 (Los)**

Figure D-27 - Study Design

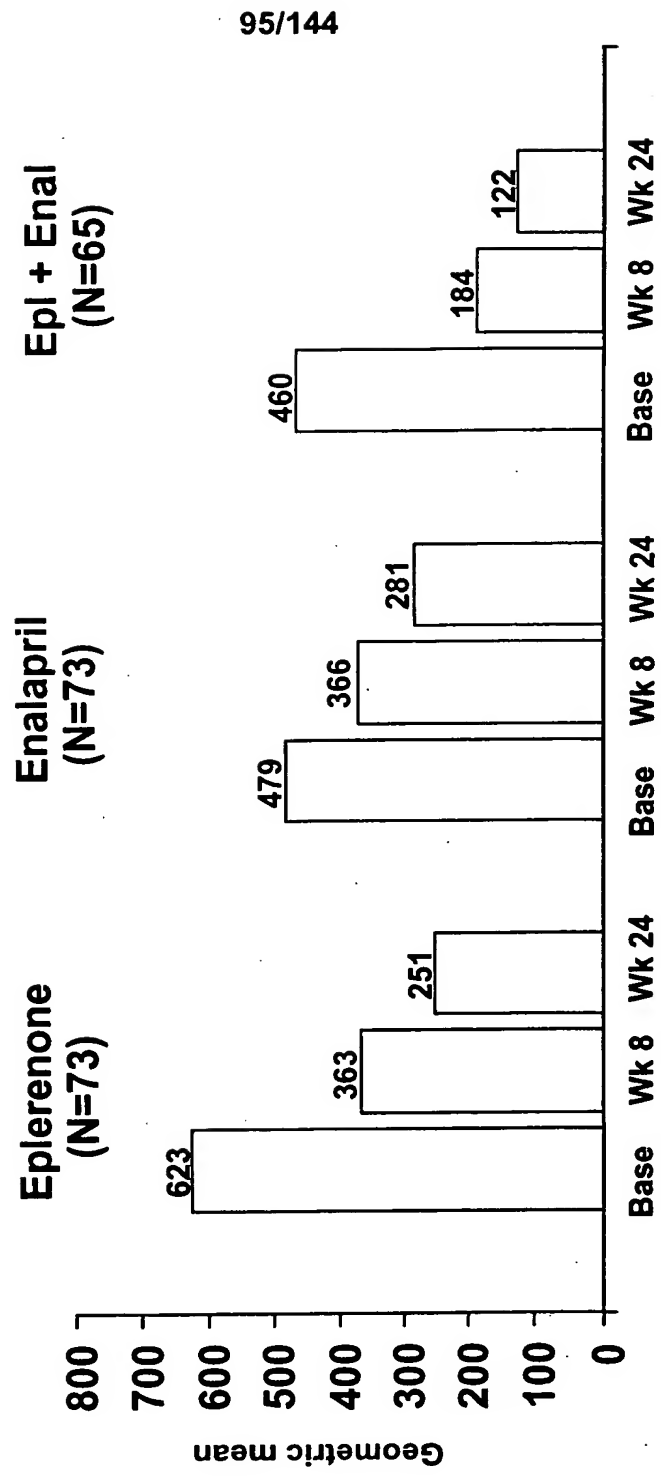


**Figure D-28 - Mean Change From Baseline:  
UACR at Week 24**

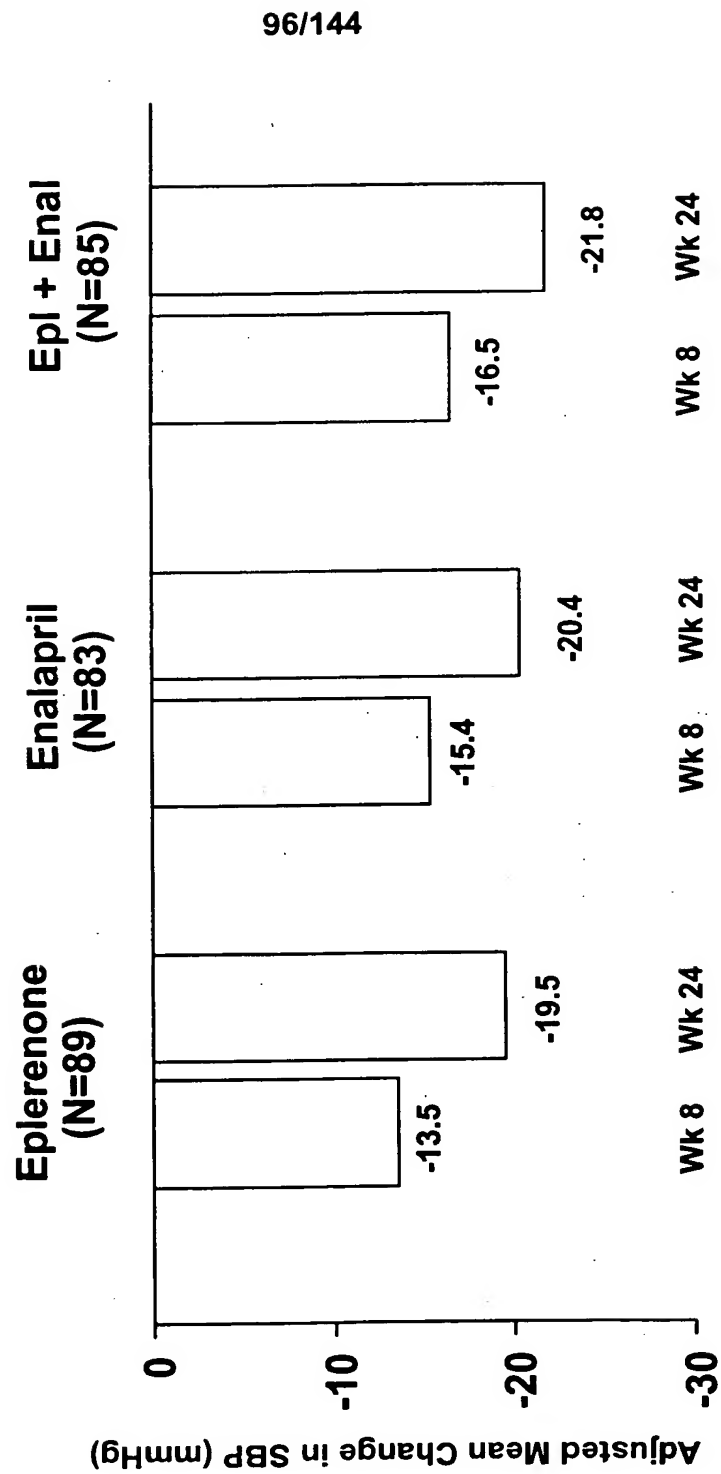


\* Adjusted for treatment, center, and baseline

Figure D-29 - Geometric Mean of UACR (ug/g)  
at Week 8 and Week 24



**Figure D-30 - Mean Change from Baseline in SBP  
at Week 8 and Week 24**





**Figure D-31 - Mean Change from Baseline in DBP  
at Week 8 and Week 24**

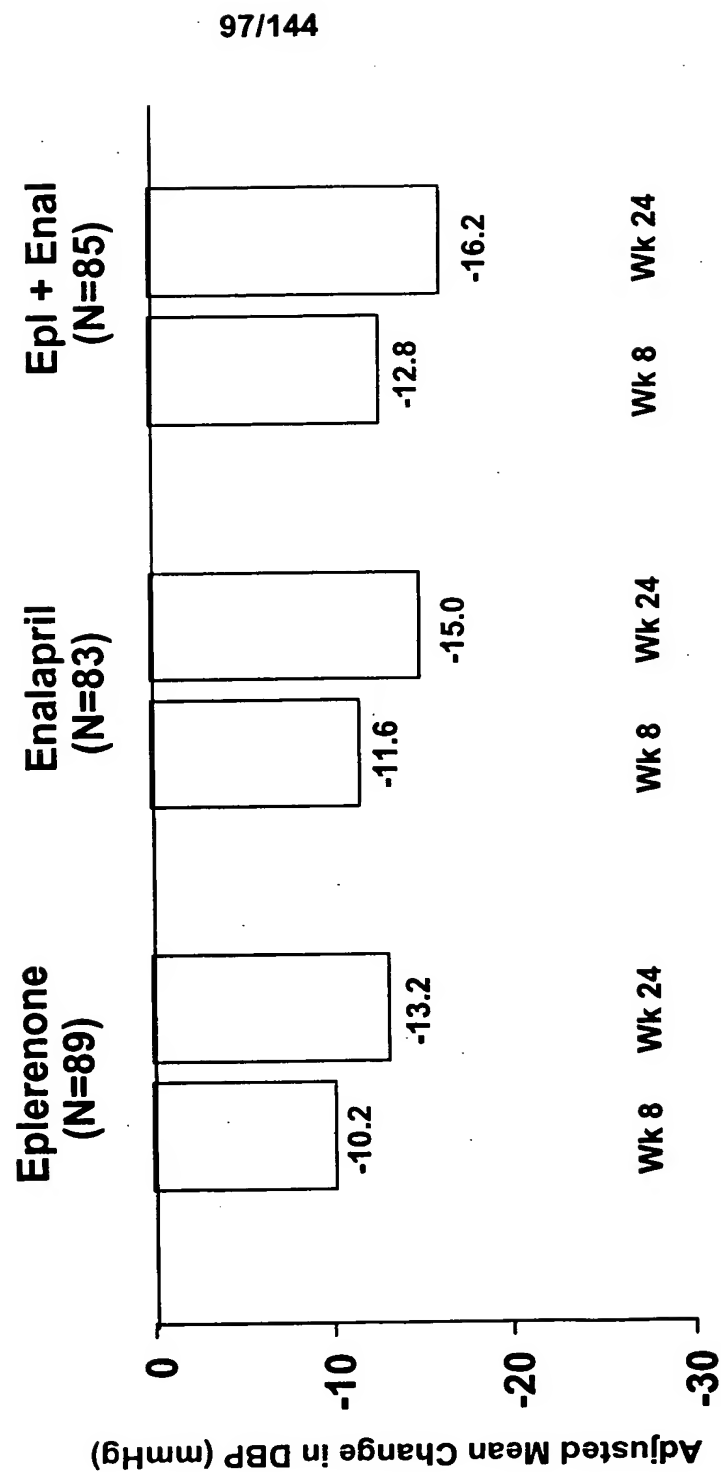
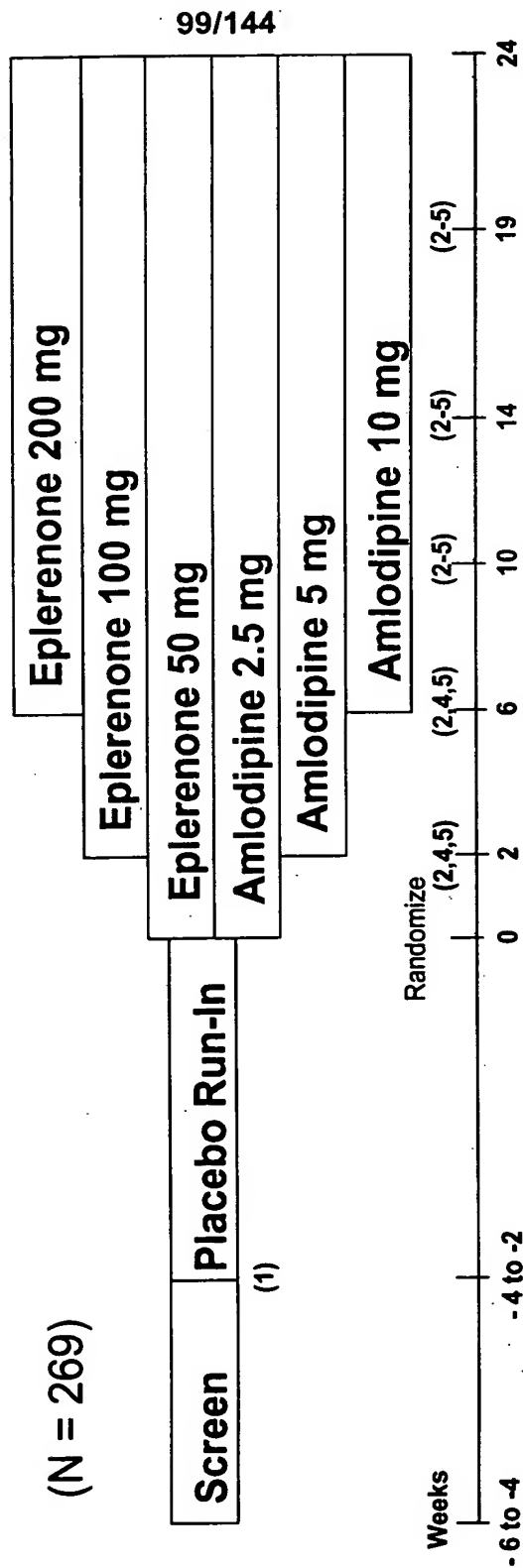


Figure D-32 - Adverse Events of Special Interest

AEs [N(%)]	Epl (N = 93)	Enal (N = 84)	Epl + Enal (N = 89)
Hyperkalemia	15 (16.1)	5 (6.0)	21 (24.1)
Hyperuricemia	4 (4.3)	1 (1.2)	0 (0.0)
Increased Lab Values			
GGT	3 (3.2)	3 (3.6)	2 (2.3)
SGOT	2 (2.2)	1 (1.2)	1 (1.1)
SGPT	2 (2.2)	2 (2.4)	1 (1.1)
BUN	5 (5.4)	0 (0.0)	3 (3.4)
Impotence	0 (0.0)	1 (2.0)	0 (0.0)
Gynecomastia	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalemia	0 (0.0)	0 (0.0)	0 (0.0)
Menstrual Abnormalities	1 (2.5)	2 (6.1)	0 (0.0)

**Figure D-33 - Eplerenone vs. Amlodipine in Elevated SBP  
Study Design**



**Figure D-34 - Eplerenone vs. Amlodipine in Elevated SBP**

**Mean Change From Baseline in BP  
(Week 24)**

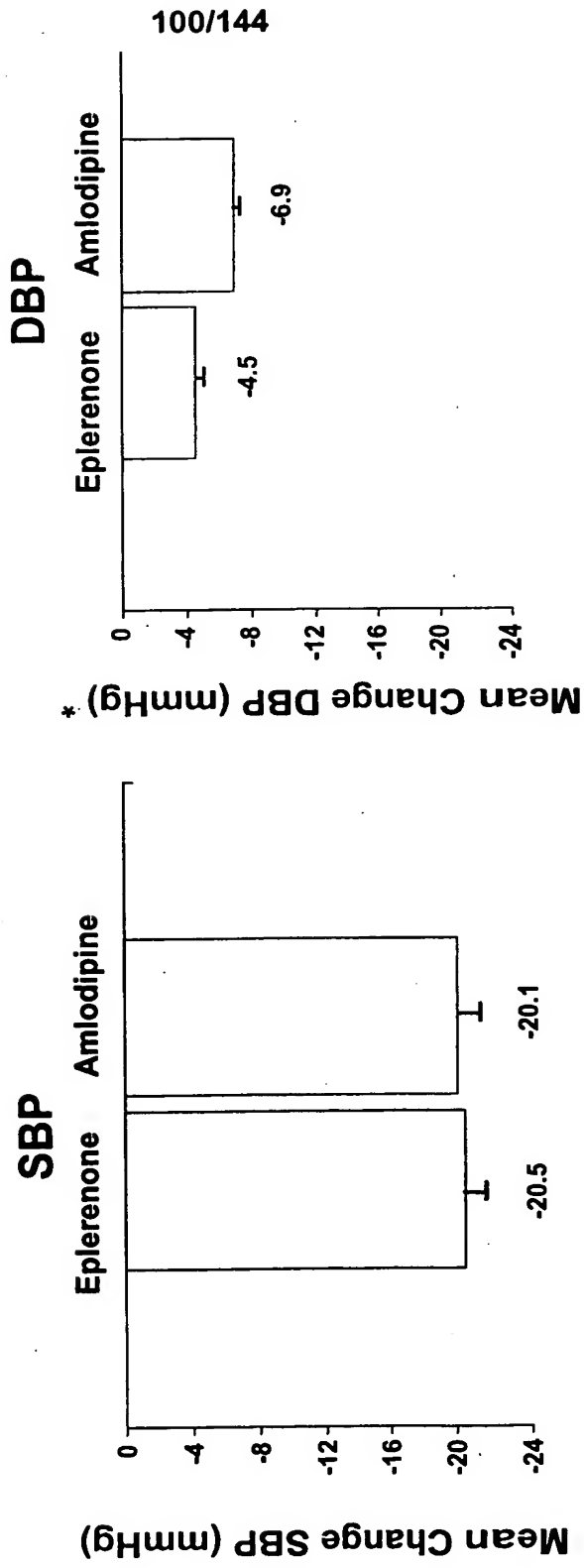
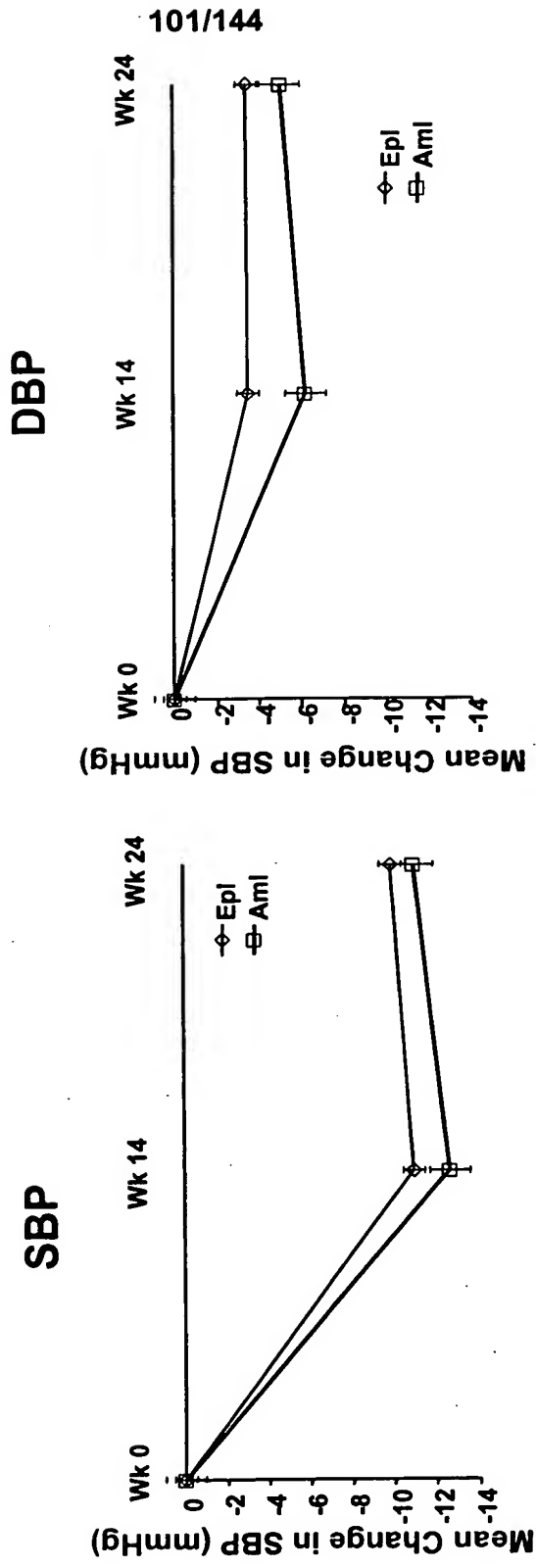


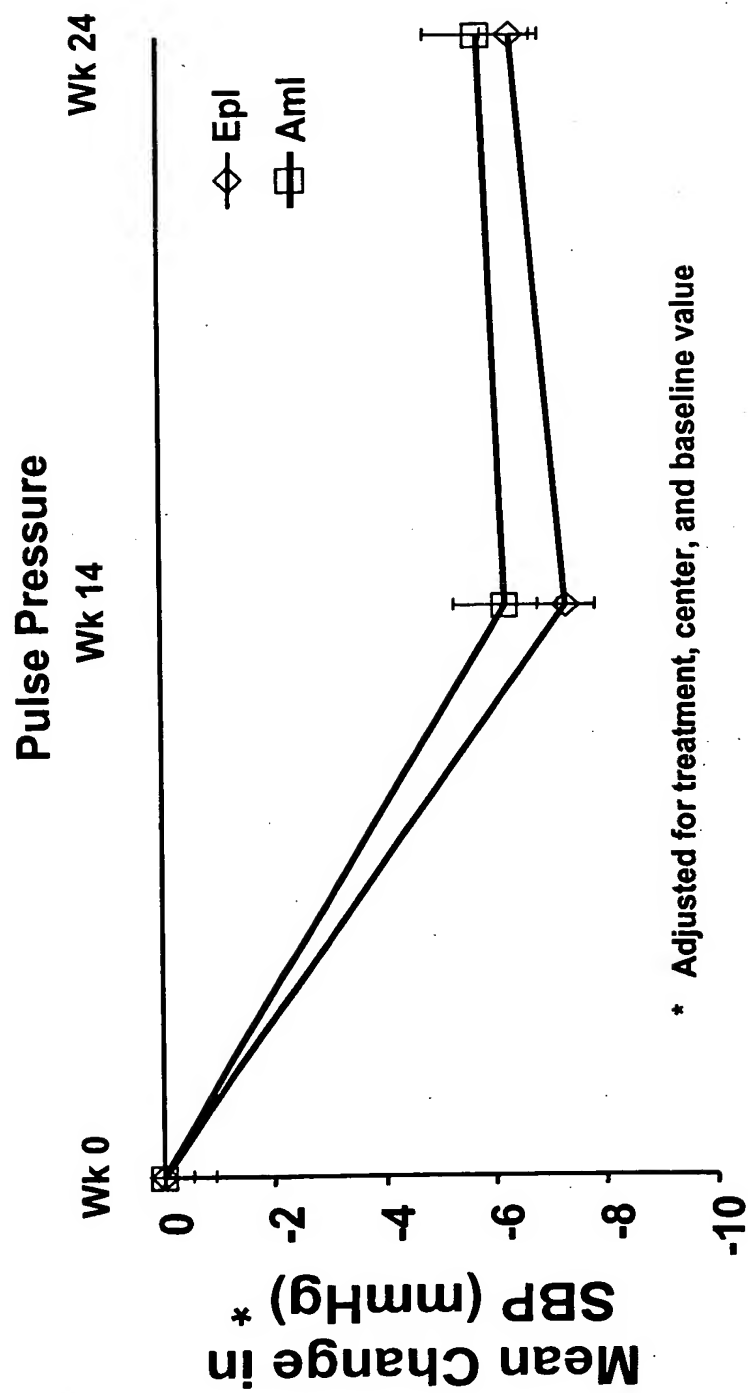
Figure D-35 - Eplerenone vs. Amlodipine in Elevated SBP

Mean Change From Baseline in 24-Hour Mean BP ABPM Measurements

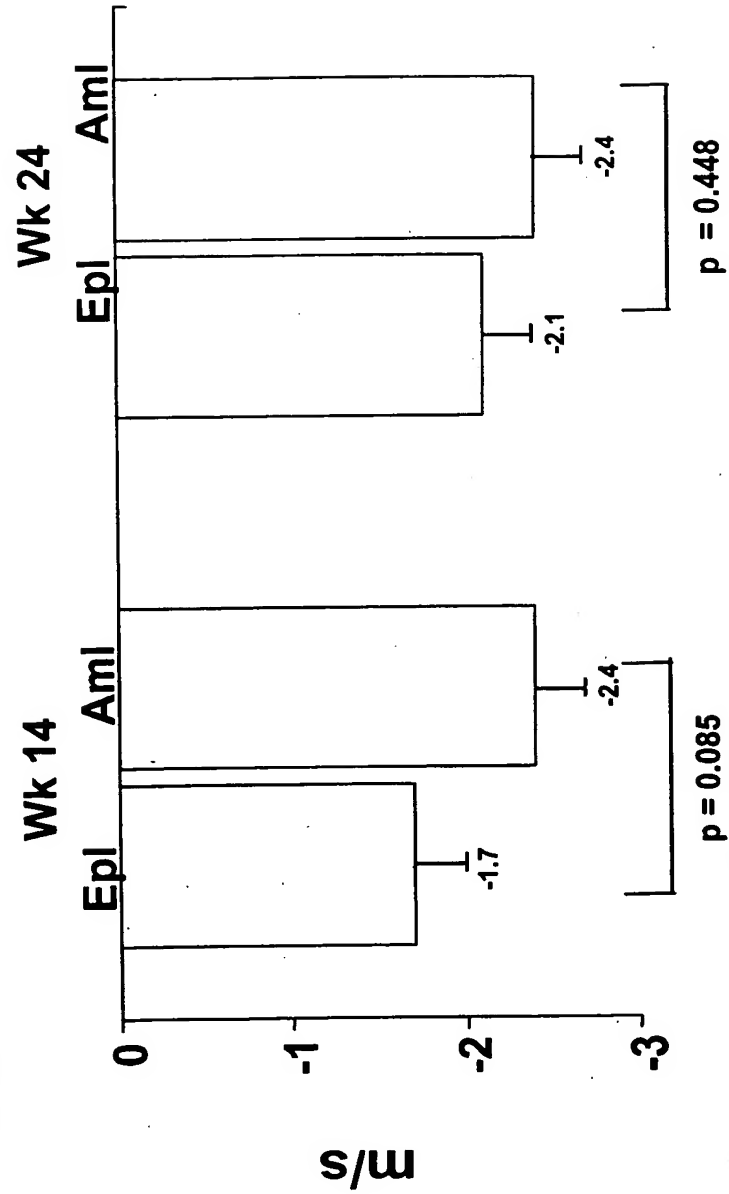


\* Adjusted for treatment, center, and baseline value

**Figure D-36 - Eplerenone vs. Amlodipine in Elevated SBP**  
Mean Change From Baseline in 24-Hour Mean PP ABPM Measurements

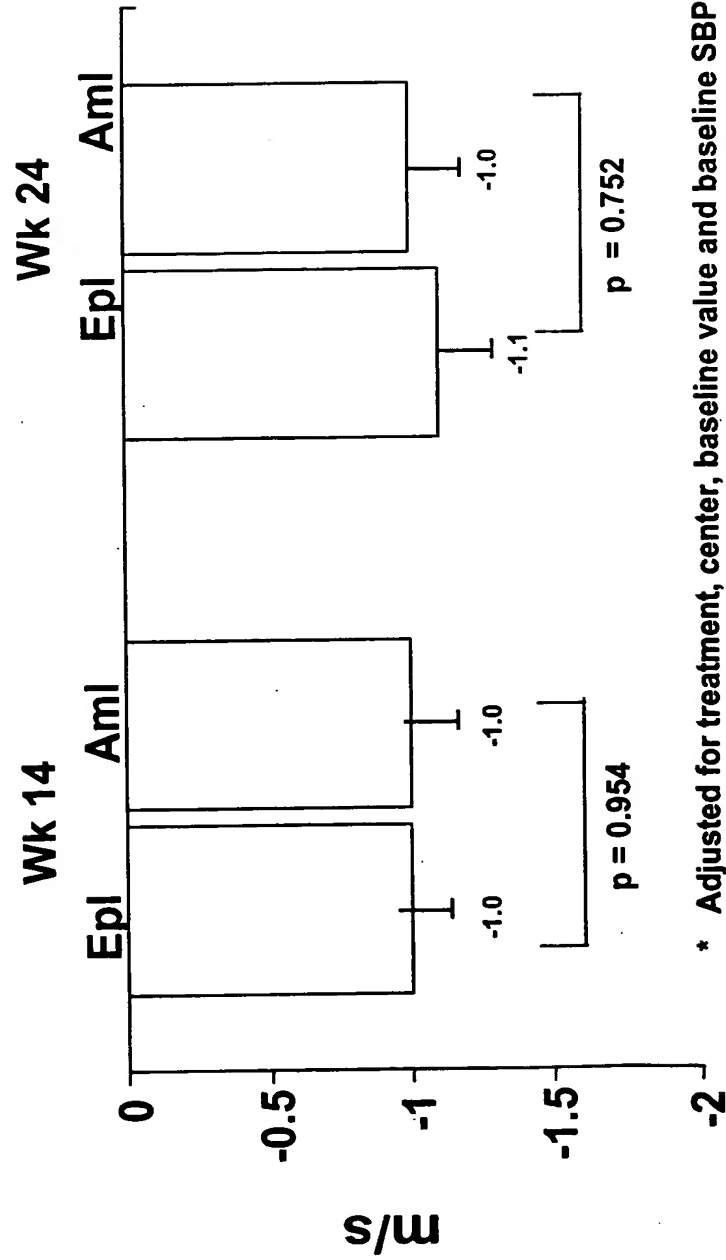


**Figure D-37 - Eplerenone vs. Amlodipine in Elevated SBP  
Mean Change From Baseline: Carotid-Femoral PWV**



\* Adjusted for treatment, center, baseline value and baseline SBP

**Figure D-38 - Eplerenone vs. Amlodipine in Elevated SBP  
Mean Change From Baseline: Carotid-Radial PWV**



\* Adjusted for treatment, center, baseline value and baseline SBP



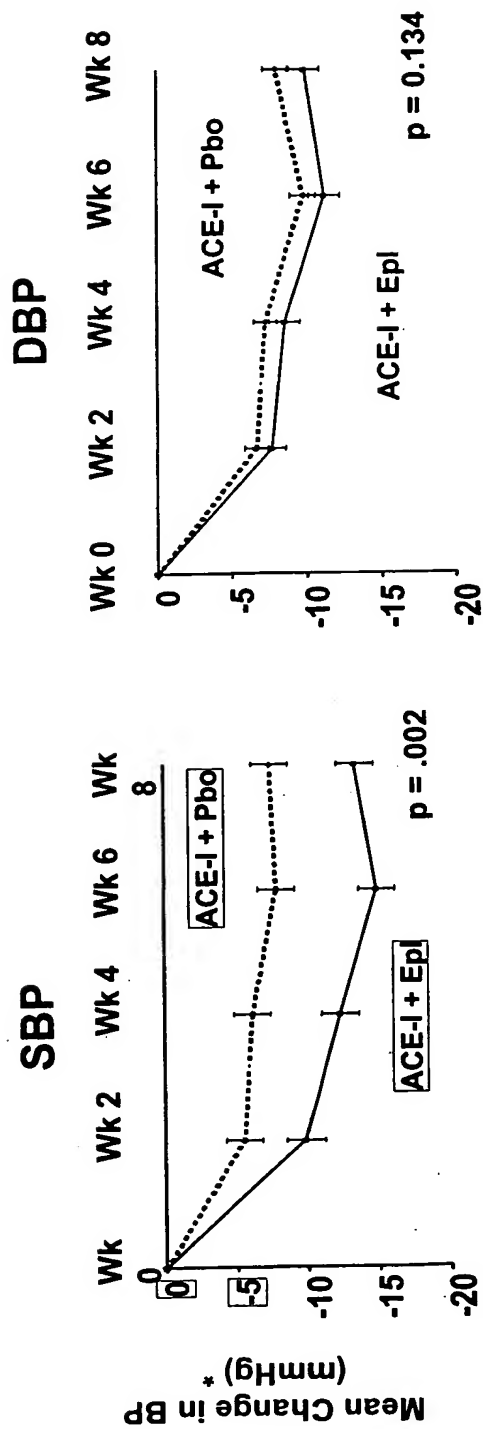
**Figure D-39 - Eplerenone vs. Amlodipine in Elevated SBP  
Adverse Events of Special Interest**

<u>AEs [N(%)]</u>	<u>EPL</u> (N = 134)	<u>AMI</u> (135)
Hyperkalemia	2 (1.5)	1 (1.7)
Hyperuricemia	1 (0.7)	0 (0.0)
Increased Lab Values		
GGT	0 (0.0)	0 (0.0)
SGOT	0 (0.0)	0 (0.0)
SGPT	0 (0.0)	0 (0.0)
BUN	0 (0.0)	0 (0.0)
Impotence*	2 (3.3)	0 (0.0)
Gynecomastia	0 (0.0)	0 (0.0)
Hypotension	0 (0.0)	1 (0.7)
Hypokalemia	0 (0.0)	2 (1.5)
Menstrual Irregularities	0 (0.0)	0 (0.0)
Edema Peripheral	6 (4.5)	34 (25.2)

\* N = 61 (EPL); 66 (AML)

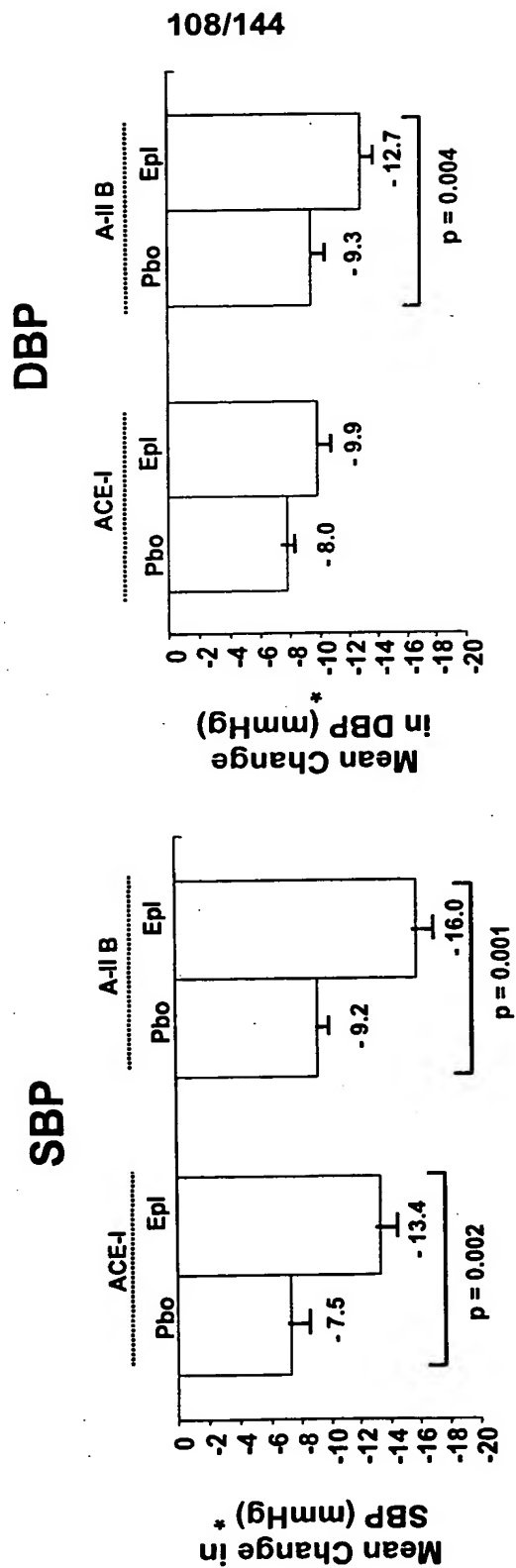


Figure D-41: Mean Change in BP (Each Visit) in Patients not controlled with ACE-I



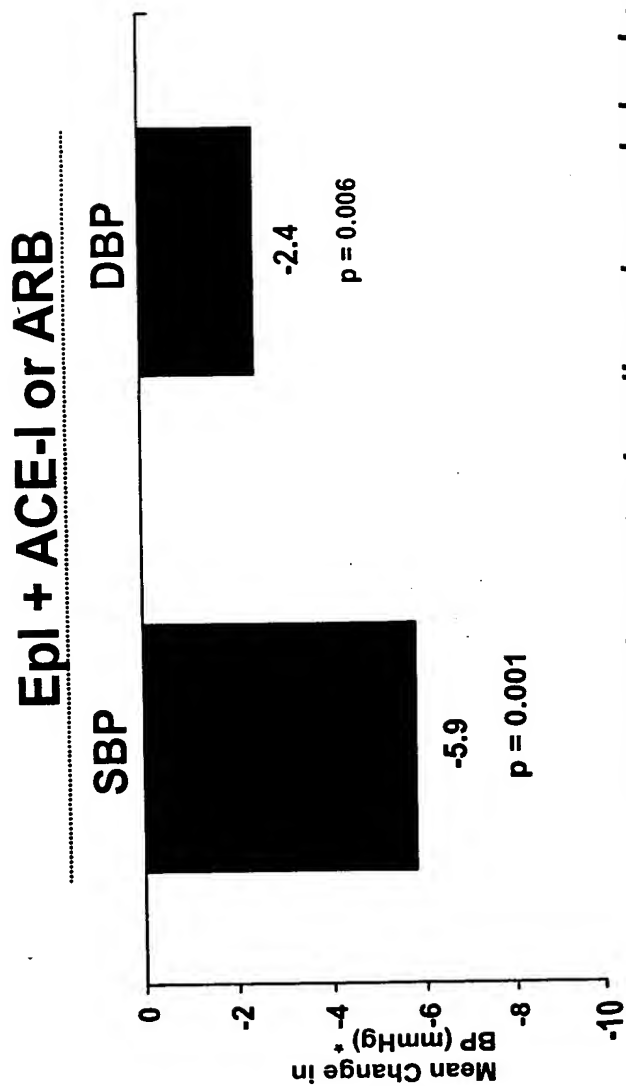
\*Adjusted to treatment, center, and baseline value

**Figure D-42 - Co-Administration with ACE-I or ARB**  
**Mean Change From Baseline in BP**  
**Week 8 (Final Visit)**



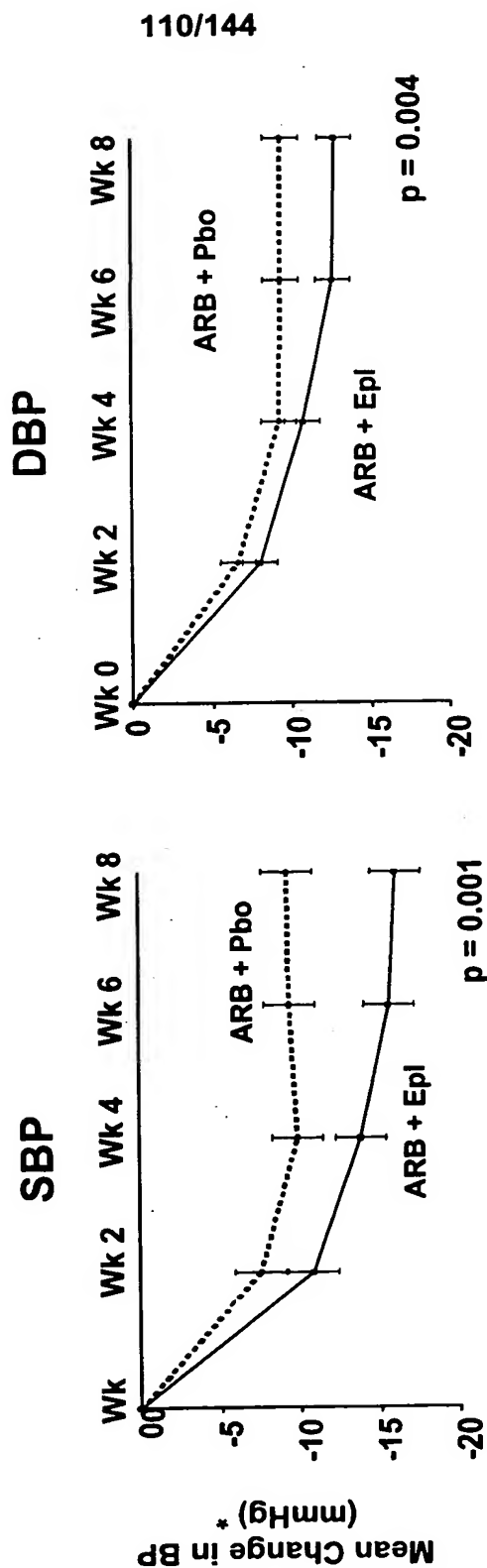
\* Adjusted to treatment, center, and baseline value

Figure D-43: Mean Change From Baseline in BP  
Week 8 (Final Visit)



*\*Adjusted to center, baseline value, and placebo-corrected*

Figure D-44: Mean Change in BP (Each Visit) in Patients not controlled with ARB



\*Adjusted to treatment, center, and baseline value

**Figure D-45: Mean Change From Baseline:  
Laboratory Values**

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Lab Values (Stderr)	ACE-I		ARB	
	Pbo (N = 90)	Epl (N = 87)	Pbo (N = 81)	Epl (N = 83)
AST (SGOT)	0.9 (0.4)	0.6 (0.8)	7.3 (7.0)	0.8 (0.8)
ALT (SGPT)	1.0 (0.8)	1.2 (1.5)	8.1 (8.1)	2.1 (1.1)
Creatinine	1.7 (1.2)	1.0 (1.2)	0.4 (1.3)	4.4 (1.5)
BUN	-0.02 (0.14)	0.06 (0.15)	0.02 (0.19)	0.73 (0.20)*
Na	0.3 (0.3)	-0.6 (0.3)	0.2 (0.4)	-0.7 (0.4)
K*	0.03 (.04)	0.13 (0.05)	0.04 (0.04)	0.20 (0.05)*
Uric Acid	2.3 (5.4)	11.3 (7.0)	-1.8 (5.0)	25.4 (7.3)*
Mg	0.002 (0.008)	-0.003 (0.008)	-0.003 (0.007)	-0.013 (0.009)

\* p < 0.001 vs. A-II/Pbo

Figure D-46: Change in Serum Potassium Values in Patients not controlled with ACE-I

	ACE-I + Pbo			ACE-I + Epl		
	N	Baseline	Mean Change	N	Baseline	Mean Change
<b>Week 2</b>	88	4.36	0.04	82	4.30	0.10
<b>Week 4</b>	84	4.36	0.02	77	4.34	0.15
<b>W k 6</b>	77	4.36	0.09	71	4.32	0.16
<b>Week 8</b>	55	4.38	0.03	59	4.32	0.13



Figure D-47: Change in Serum Potassium Values in Patients not controlled with ARB

	ARB + Pbo			ARB + Epl		
	N	Baseline	Mean Change	N	Baseline	Mean Change
<b>Week 2</b>	78	4.29	0.01	82	4.31	0.18
<b>Week 4</b>	76	4.29	0.01	79	4.31	0.19
<b>Week 6</b>	72	4.29	0.01	68	4.33	0.21
<b>Week 8</b>	58	4.26	0.04	62	4.31	0.20

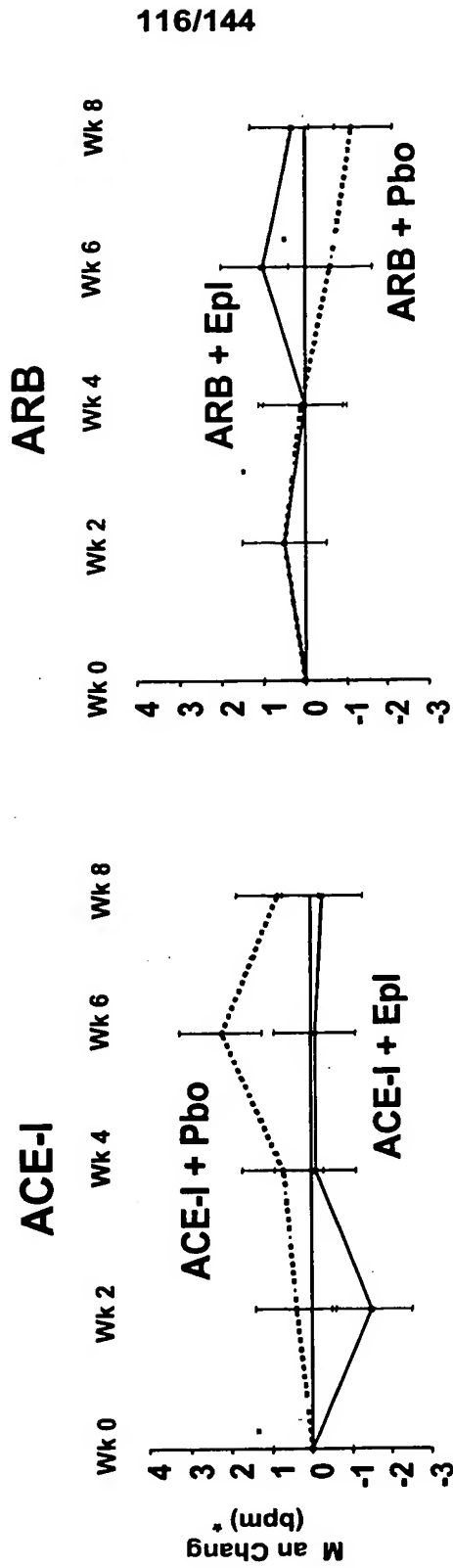
Figure D-48: Adverse Events of Interest

[N (%)]	ACE-I		ARB	
	Pbo (N = 90)	Epl (N = 87)	Pbo (N = 81)	Epl (N = 83)
Aggravated Hypertension	0	1 (1.1)	0	0
Hyperkalemia	0	1 (1.1)	0	0
Hyperuricemia	0	1 (1.1)	0	2 (2.4)
Increased Lab Values				
GGT	0	1 (1.1)	1 (1.2)	0
SGOT	0	1 (1.1)	1 (1.2)	0
SGPT	0	1 (1.1)	1 (1.2)	1 (1.2)
BUN	0	0	0	1 (1.2)
Impotence	0	0	0	1 (2.4)
Gynecomastia	0	0	0	0
Hypotension	0	0	0	1 (1.2)
Menstrual Abnormalities	0	0	0	0

Figure D-49: Serious Adverse Events

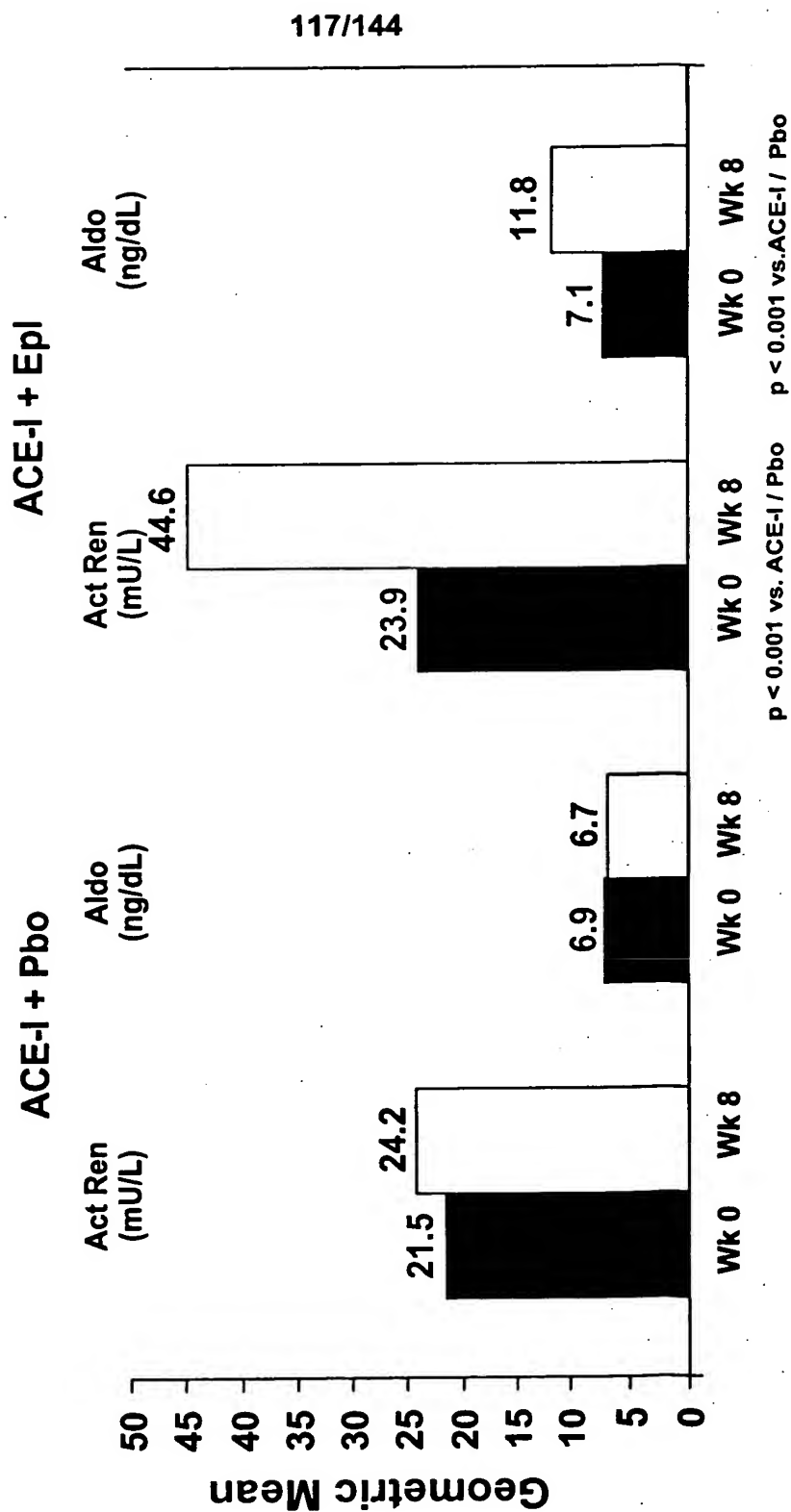
	ACE-I		ARB	
	Pbo (N = 90)	Epl (N = 87)	Pbo (N = 81)	Epl (N = 83)
Sudden Death	0	1	0	0
Aggravated HTN	0	1	0	0
Syncope	1	0	0	0
Inguinal Hernia	0	1	0	0

Figure D-50: Mean Change in Heart Rate (Each Visit)

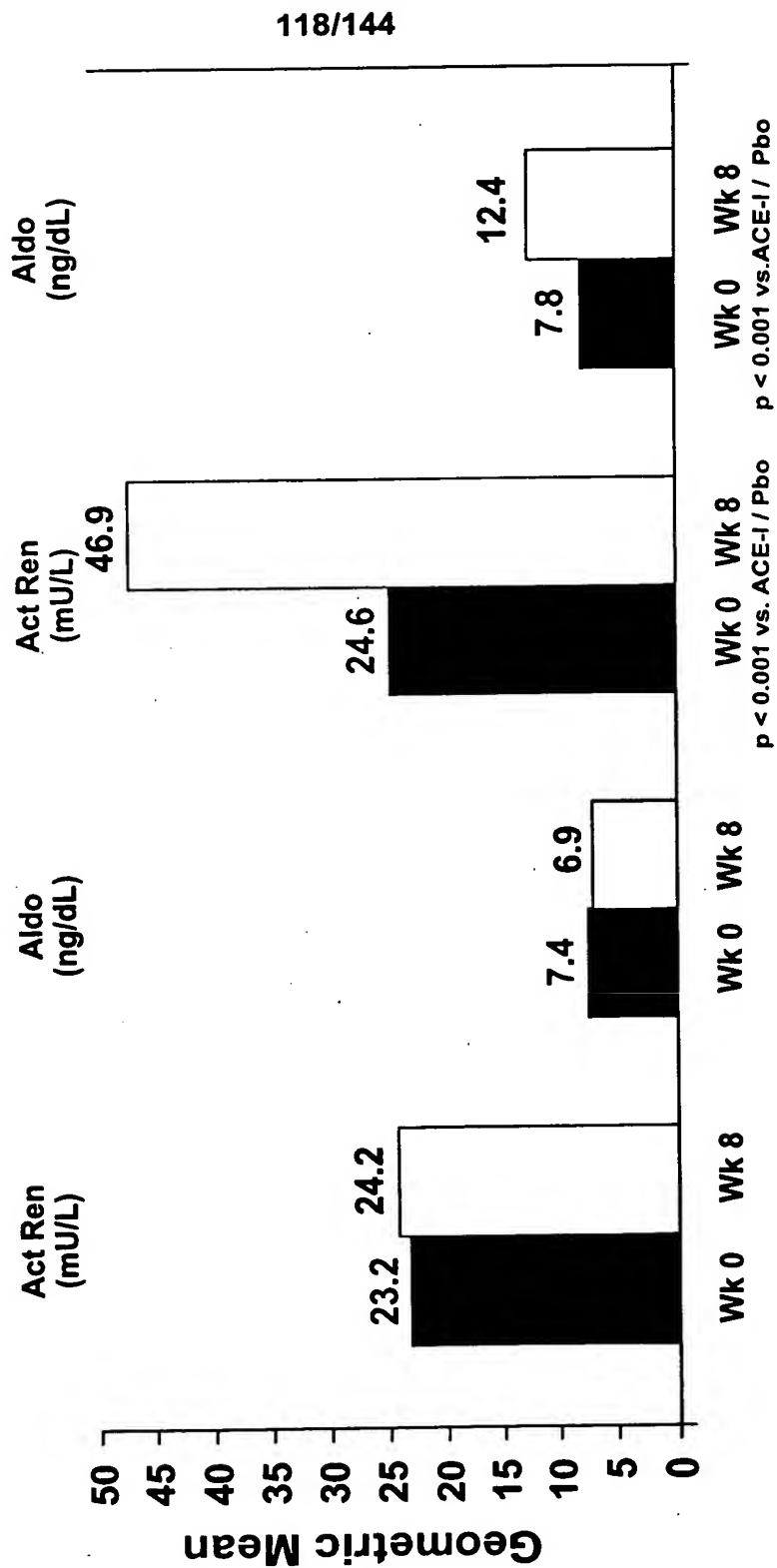


\*Adjusted to treatment, center, and baseline value

**Figure D-51: Mean Active Renin and Aldosterone Levels**



**Figure D-52: Mean Active Renin and Aldosterone Levels**  
**ARB + Pbo**      **ARB + Epl**



**Figure D-53: Reason For Withdrawal**

	ACE-I		ARB	
	Pbo (N = 90)	Epl (N = 87)	Pbo (N = 81)	Epl (N = 83)
<b>[N (%)]</b>				
<b>Adverse Event</b>	2 (2.2)	2 (2.3)	0 (0.0)	1 (1.2)
<b>Treatment Failure</b>	26 (28.9)	15 (17.2)	17 (21.0)	8 (9.6)
<b>Lost to Follow-up</b>	0 (0.0)	3 (3.4)	0 (0.0)	1 (1.2)
<b>Protocol Non-Compliance</b>	1 (1.1)	1 (1.1)	0 (0.0)	3 (3.6)
<b>Pre-Existing Violation</b>	1 (1.1)	4 (4.6)	0 (0.0)	0 (0.0)
<b>Other</b>	2 (2.2)	1 (1.1)	2 (2.5)	4 (4.8)

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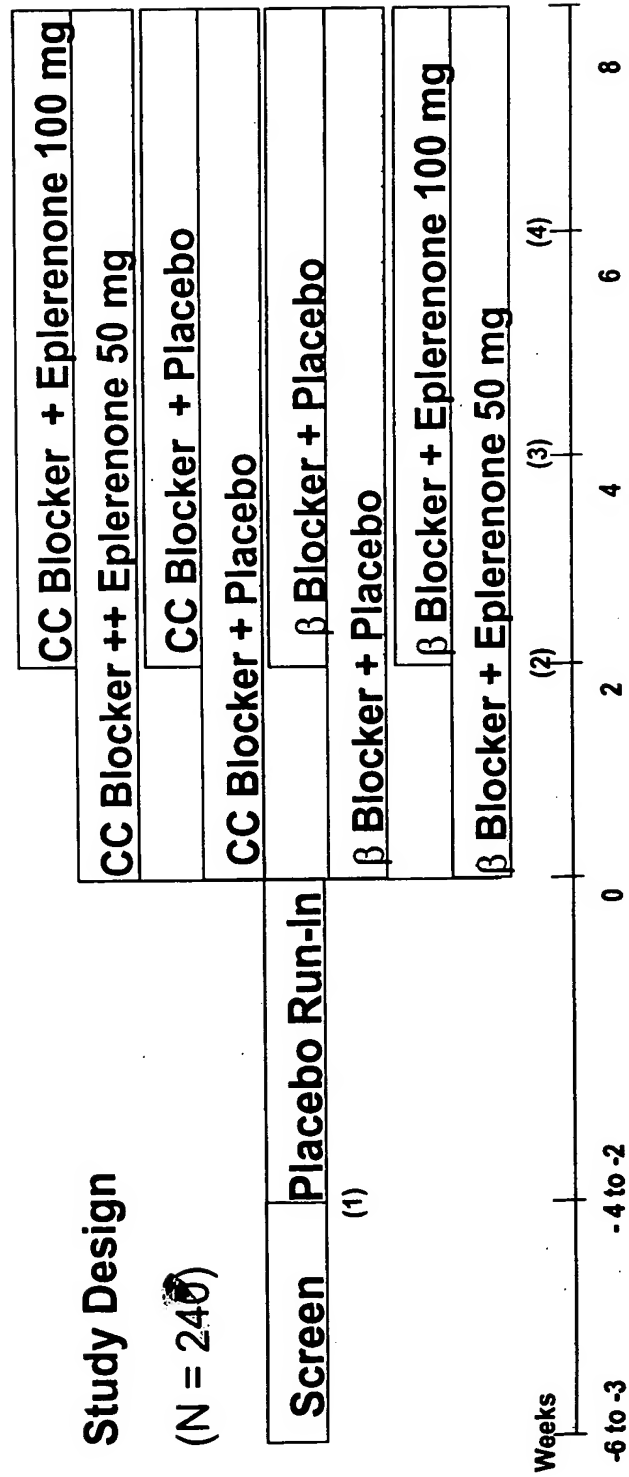
Figure D-54: Percent of Patients Responding to Treatment:  
DBP

Week	ACE-I			ARB		
	Pbo (N = 89)	Epl (N = 85)	% Difference	Pbo (N = 80)	Epl (N = 82)	% Difference
2	44.9	47.6	2.7	48.8	54.9	6.1
4	46.1	57.6	11.5	67.5	74.4	6.9
6	60.7	72.9	12.2	71.3	90.2	18.9
8 (Final)	55.1	62.4	7.3	73.8	87.8	14.0

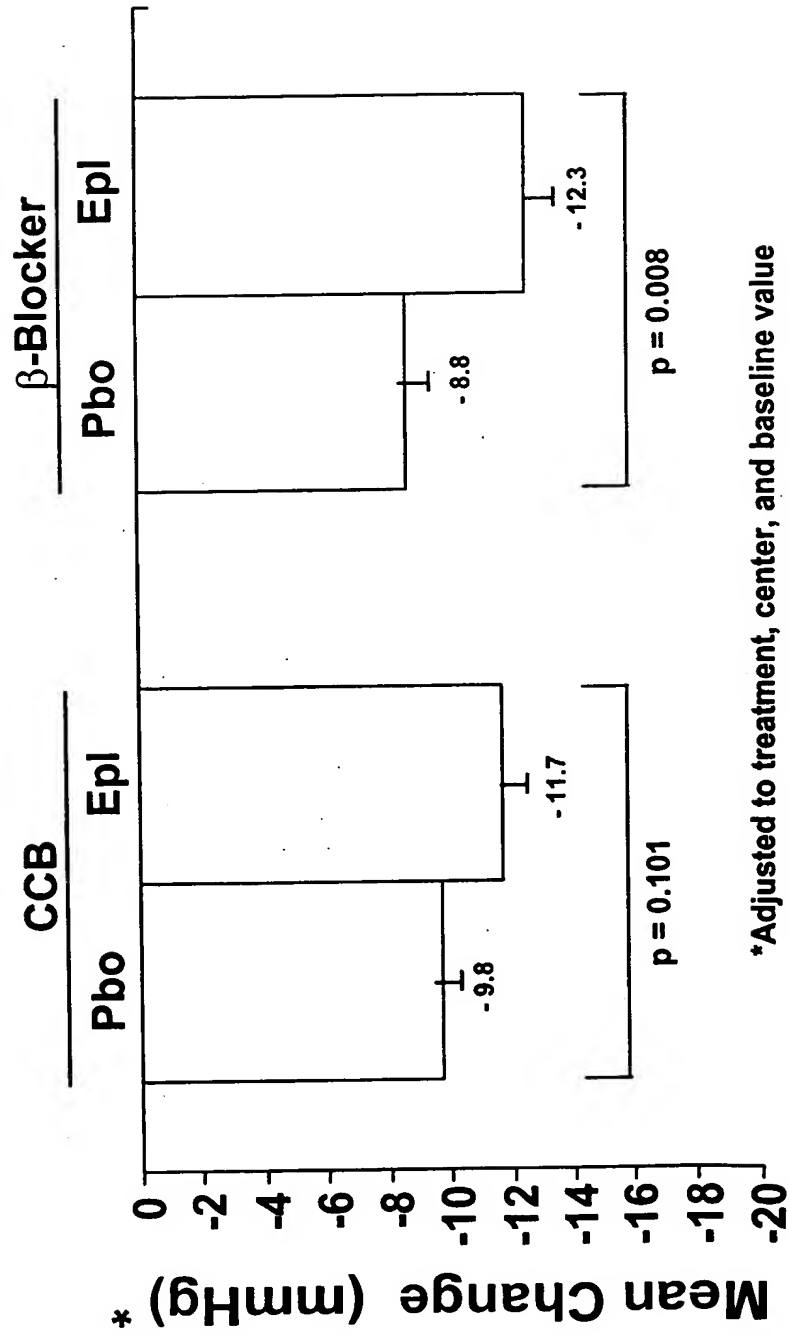
Note: Responder defined as seDBP < 90 mmHg or > 90 but a  $\geq$  10 mmHg reduction from baseline



Figure D-55 - Co-administration with CCB and  $\beta$ -Blocker

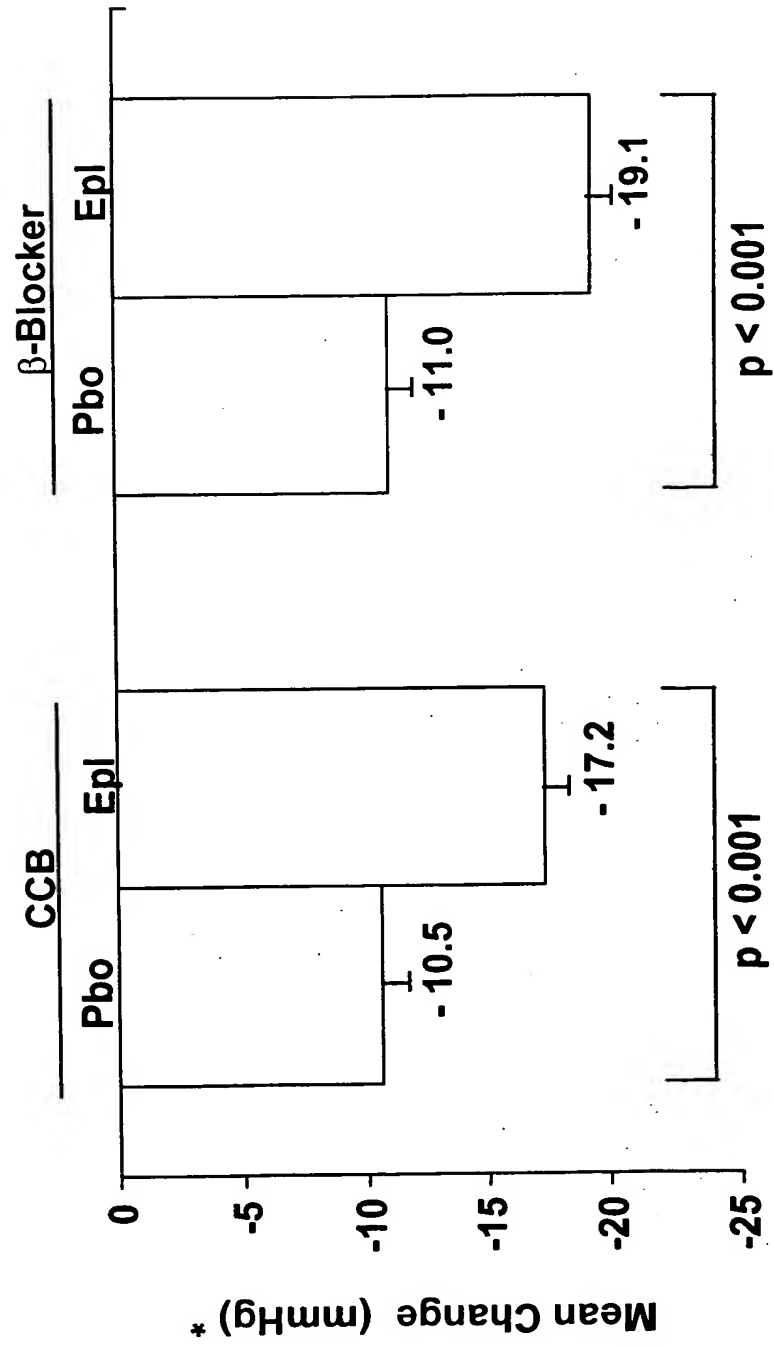


**Figure D-56 - Co-Administration with CCB or  $\beta$ -Blocker**  
 Mean Change in DBP: Baseline vs. Final Visit



\*Adjusted to treatment, center, and baseline value

**Figure D-57 - Co-Administration with CCB or  $\beta$ -Blocker**  
**Mean Change in SBP: Baseline vs. Final Visit**

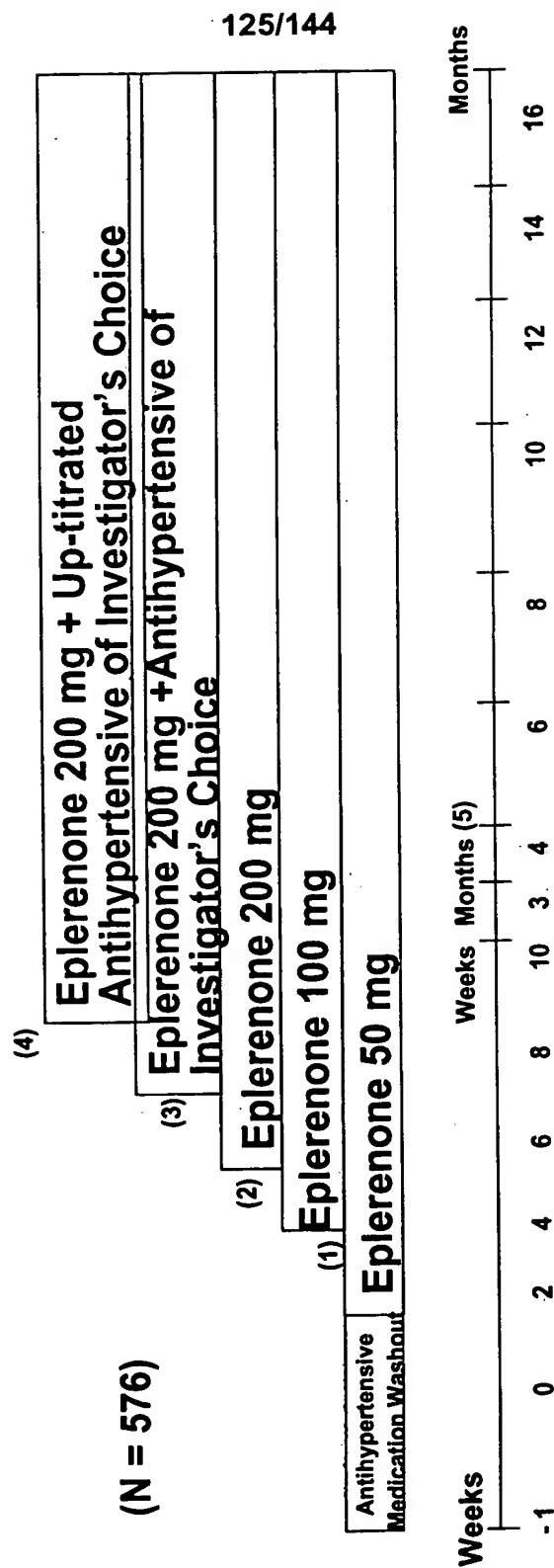


\*Adjusted to treatment, center, and baseline value

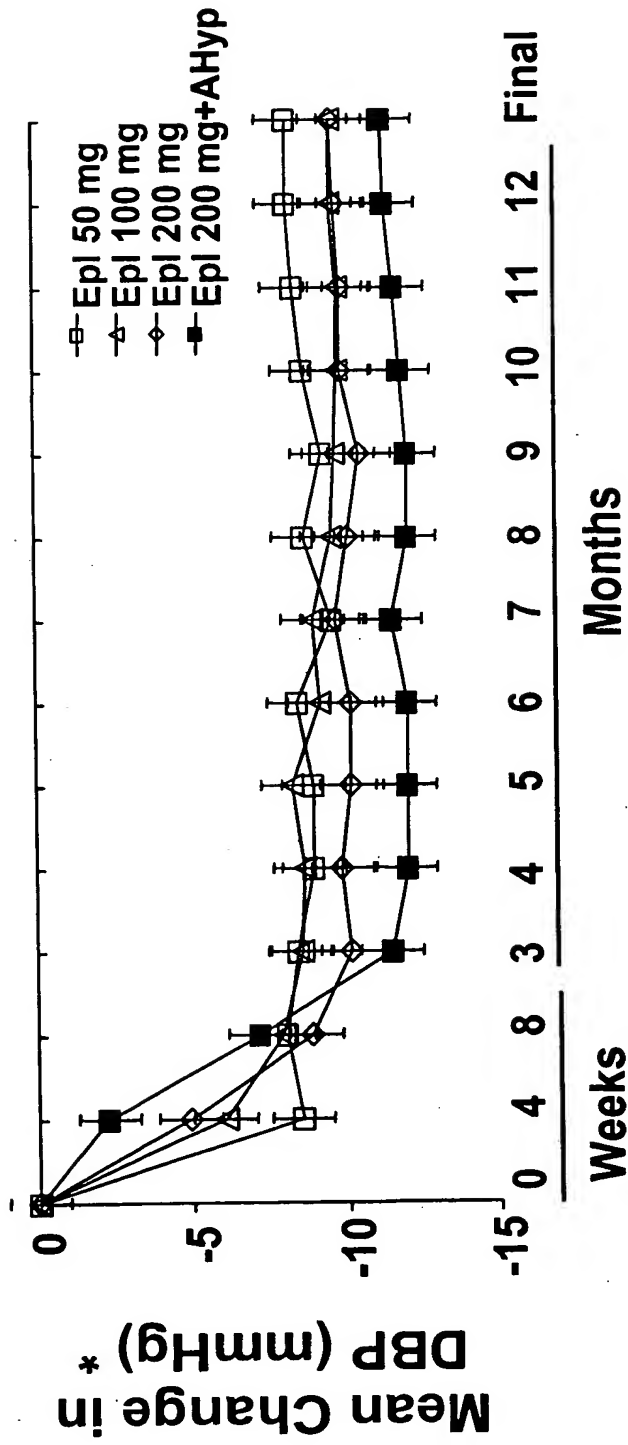
**Figure D-58 - Co-Administration with CCB or  $\beta$ -Blocker  
Adverse Events of Special Interest**

Adverse Events	CCB		$\beta$ -Blocker	
	Pbo (N = 67)	Epl (N = 70)	Pbo (N = 66)	Epl (N = 69)
Hyp rkalemia	0	0	0	4
Hyperuricemia	0	0	0	0
Increased Lab Values				
GGT	0	0	0	0
SGOT	0	0	0	0
SGPT	1	0	0	0
BUN	0	0	0	0
Impotence	0	0	0	0
Gynecomastia	0	0	0	0
Menstrual Abnormalities	0	0	0	0
Hypotension	0	1	0	0

**Figure D-59 - Long-Term, Open Label Safety  
Study Design**

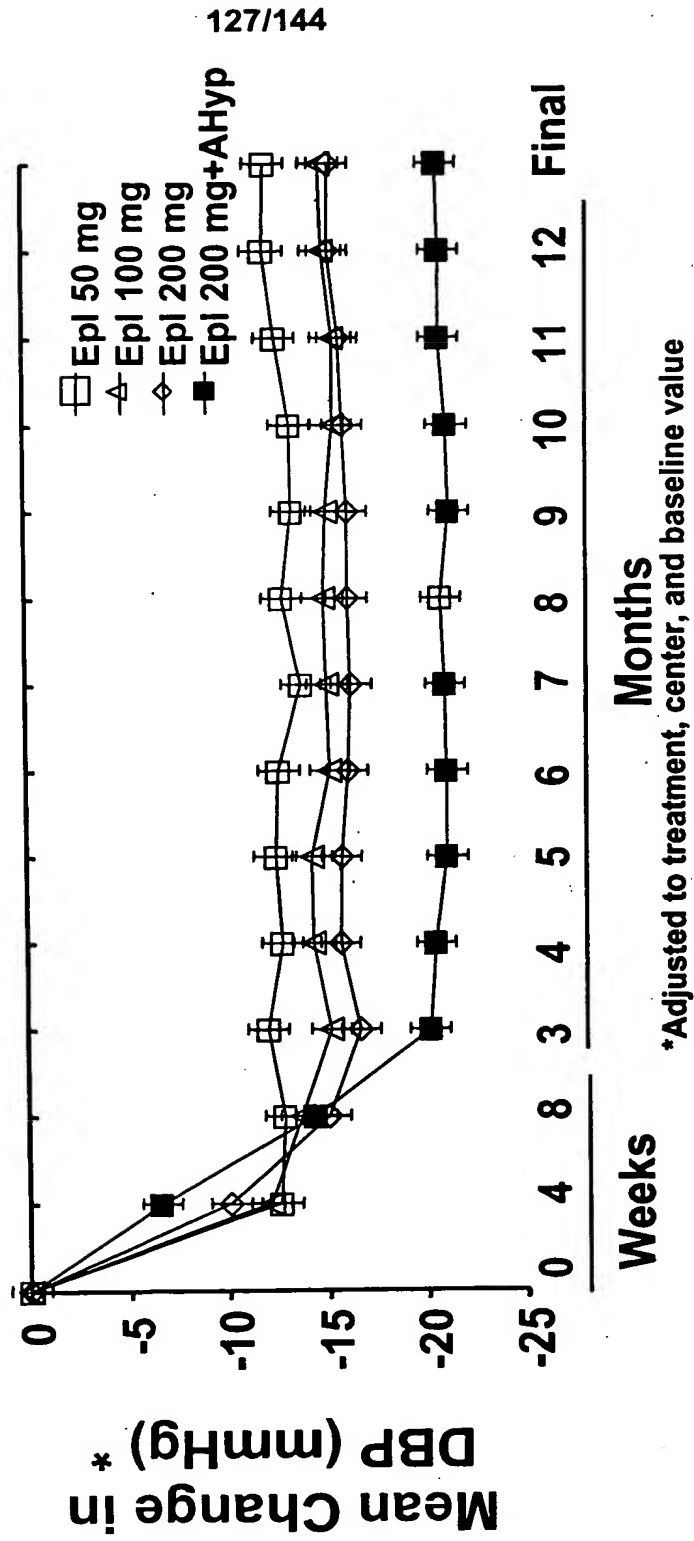


**Figure D-60 - Long-Term Open Label Safety**  
**Mean Change in DBP**



\* Adjusted to treatment, center, and baseline value

**Figure D-61 - Long-Term Open Label Safety**  
**Mean Change in SBP**



**Figure D-62 - Long-Term Open Label Safety**

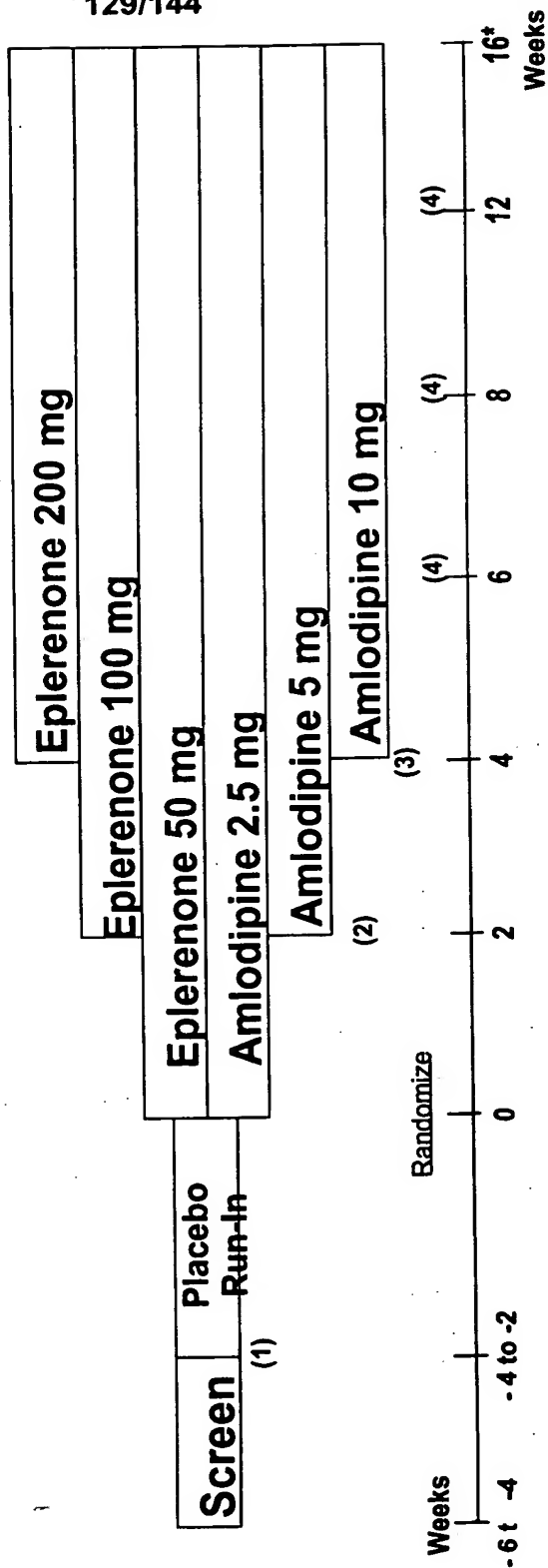
**Adverse Events of Special Interest**

<b>Adverse Event Incidence (Rate)</b>	<b>Eplerenone Doses</b>			
	<b>Combined</b>	<b>50 mg</b>	<b>100 mg</b>	<b>200 mg</b>
<b>Impotence*</b>	9 (3.0)	2	2	1
<b>Gynecomastia</b>	2 (0.3)			
<b>Hypotension</b>	2 (0.3)			
<b>Menstrual Abnormalities*</b>	3 (1.1)	2		1
<b>Hyperkalemia</b>	8 (1.4)			6

\* N = 284 (Menstrual Disorder); N = 302 (Impotence)

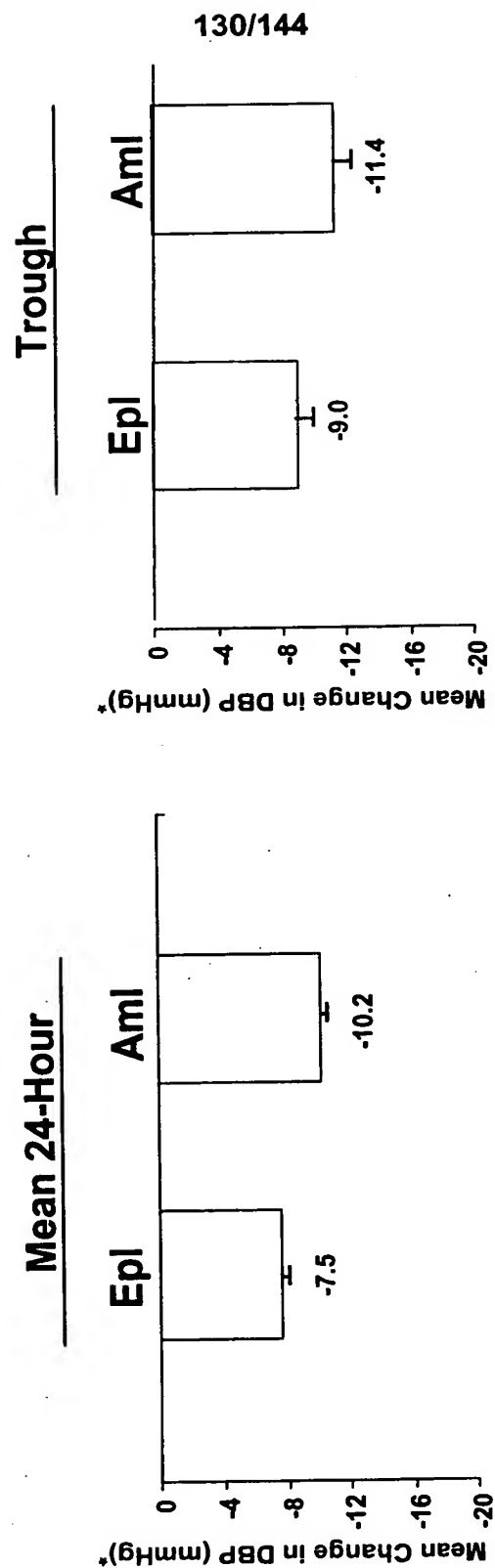


**Figure D-63 - Eplerenone vs. Amlodipine in ABPM  
Study Design**



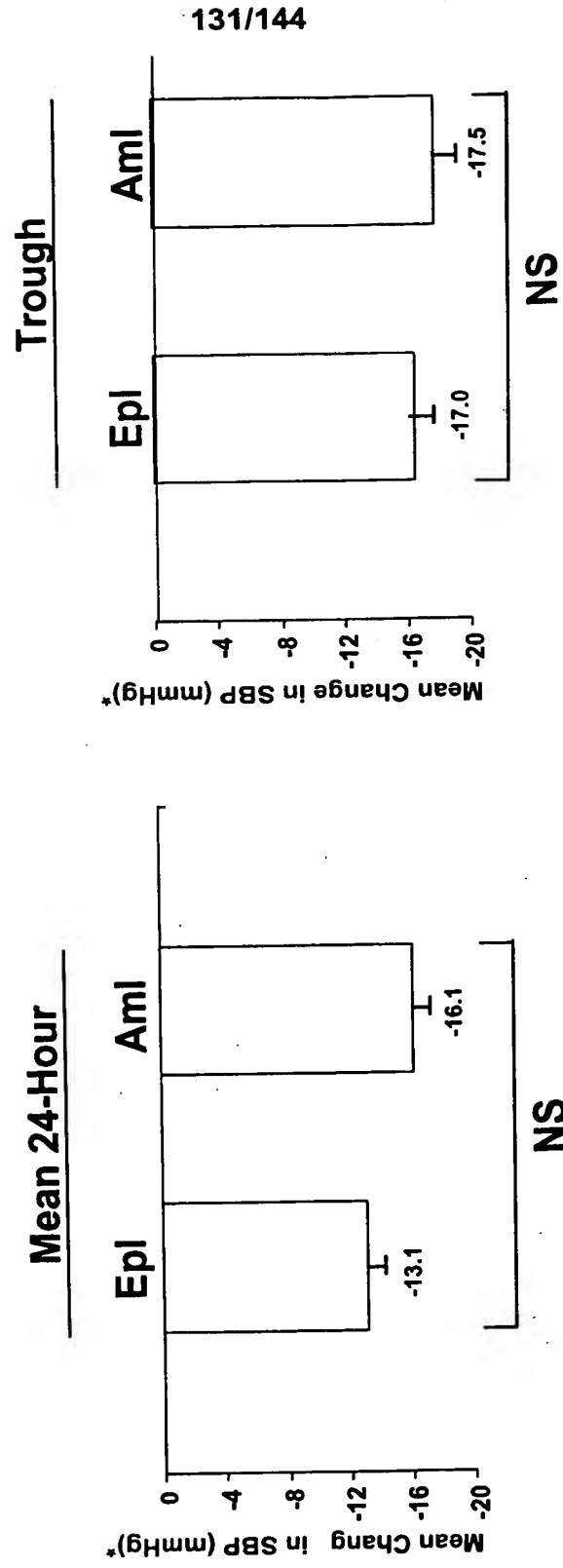
**Figure D-64 - Eplerenone vs. Amlodipine in ABPM**

**DBP: Mean Change From Baseline (ABPM)**



**Figure D-65 - Eplerenone vs. Amlodipine in ABPM**

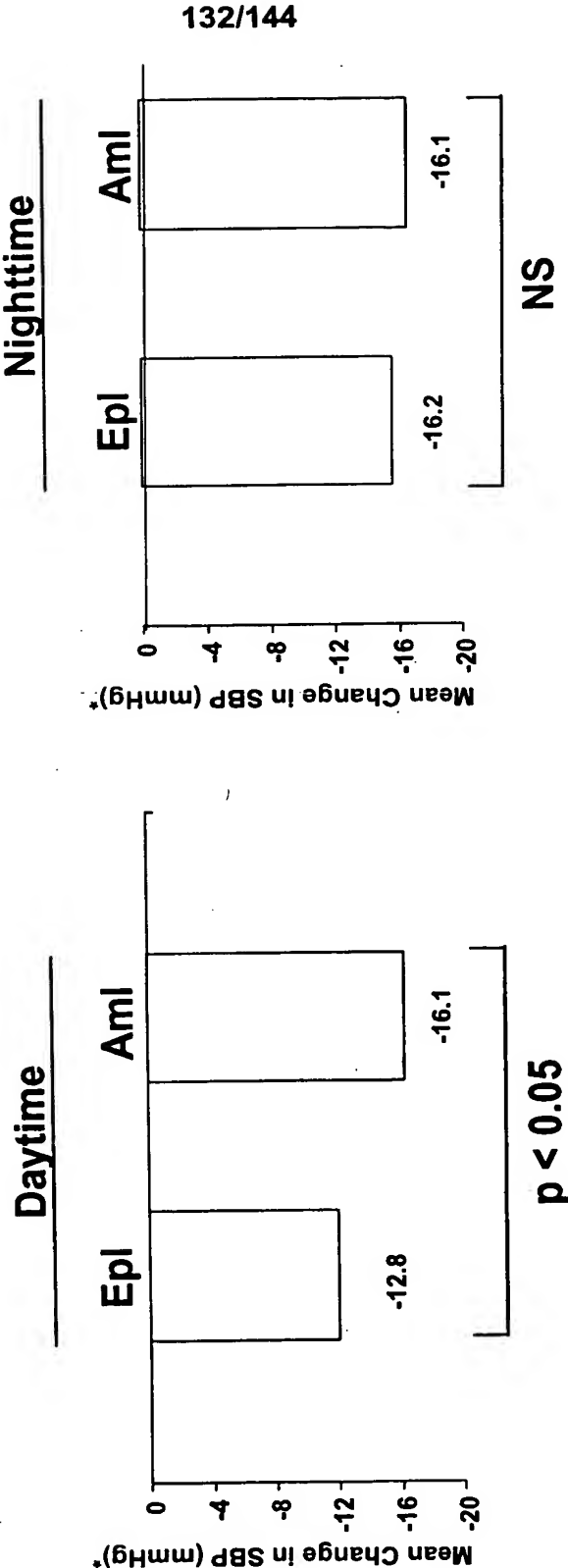
**SBP: Mean Change From Baseline (ABPM)**



\* Adjusted to treatment, center, and baseline value

**Figure D-66 - Eplerenone vs. Amlodipine in ABPM**

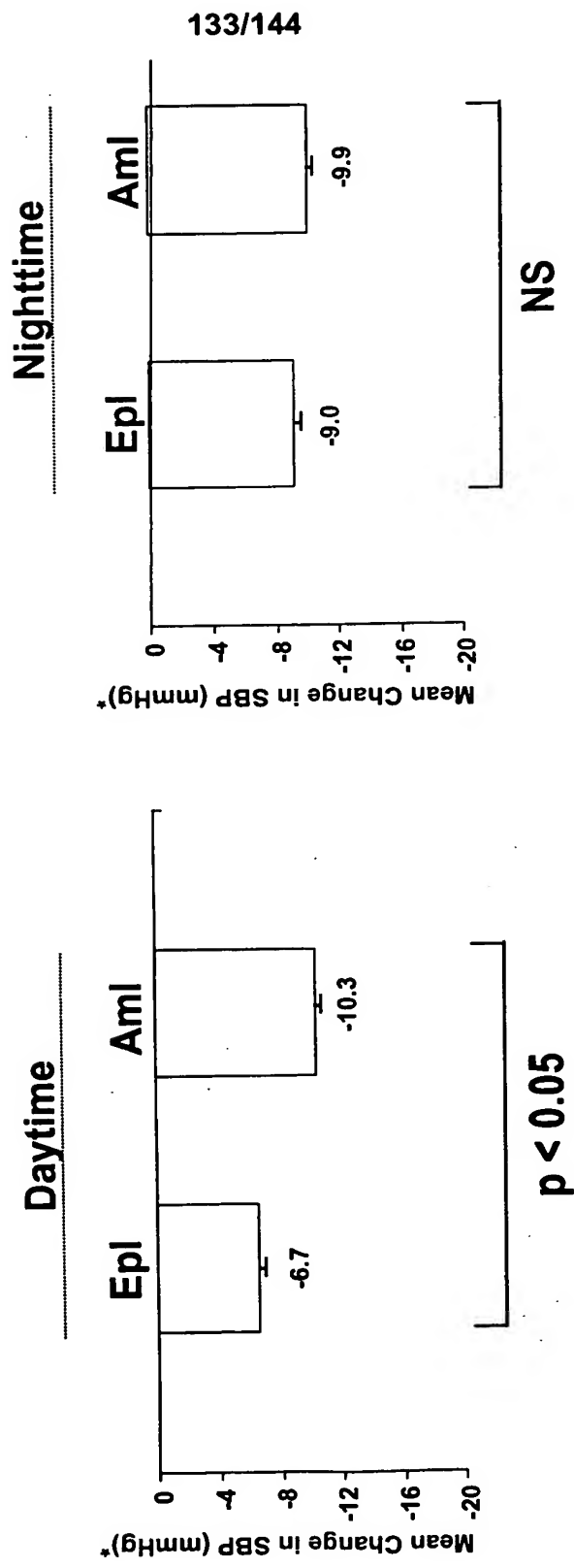
**SBP: Mean Change from Baseline  
(24-Hour ABPM)**



\* Adjusted to treatment, center, and baseline value

**Figure D-67 - Eplerenone vs. Amlodipine in ABPM**

**DBP: Mean Change from Baseline  
(24-Hour ABPM)**



\* Adjusted to treatment, center, and baseline value

**Figure D-68 - Eplerenone vs. Amlodipine in ABPM**

**SBP: Hourly Baseline Mean (24-Hour ABPM)**

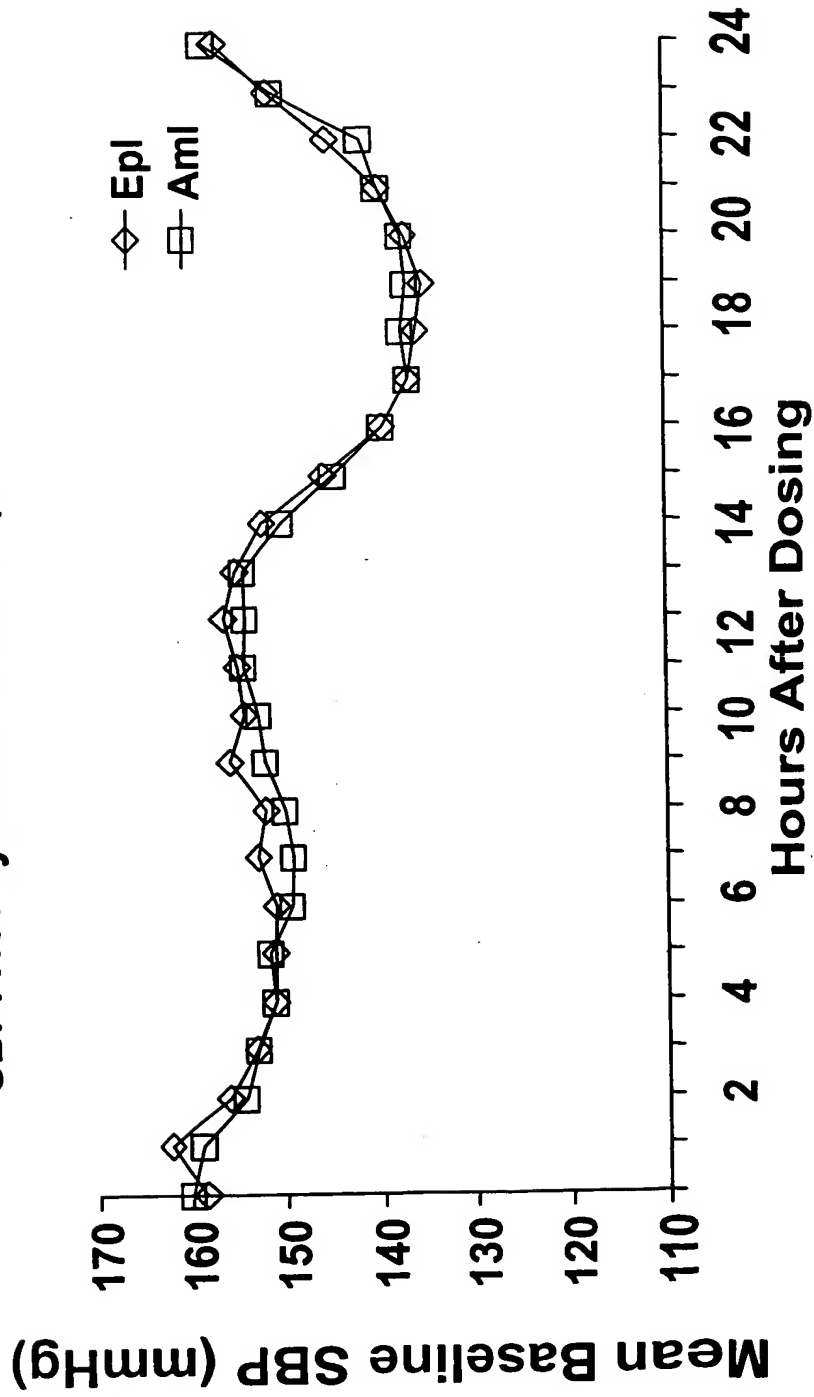
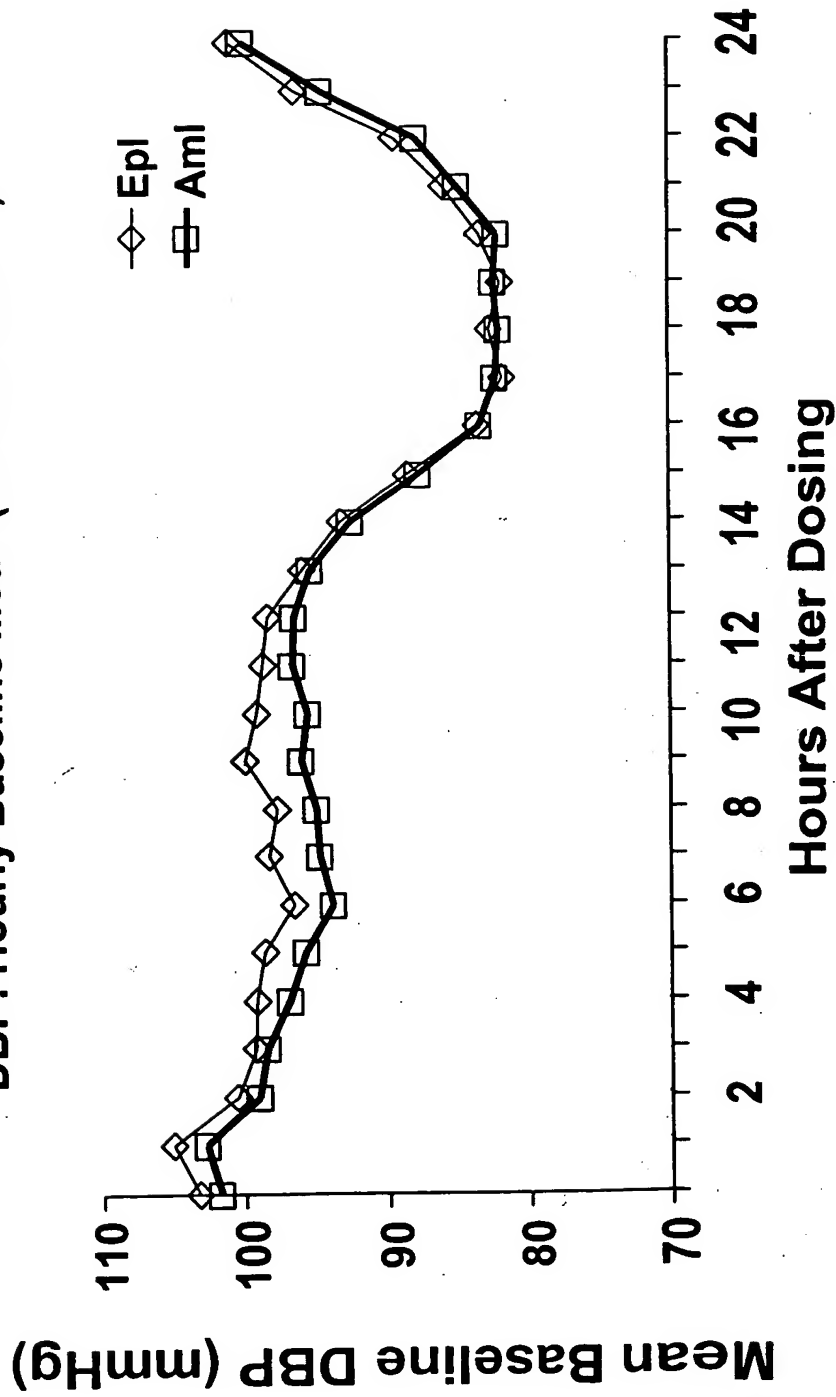


Figure D-69 - Eplerenone vs. Amlodipine in ABPM

DBP: Hourly Baseline Mean (24-Hour ABPM)



**Figure D-70 - Eplerenone vs. Amlodipine in ABPM**

**SBP: Hourly Endpoint Mean (24-Hour ABPM)**

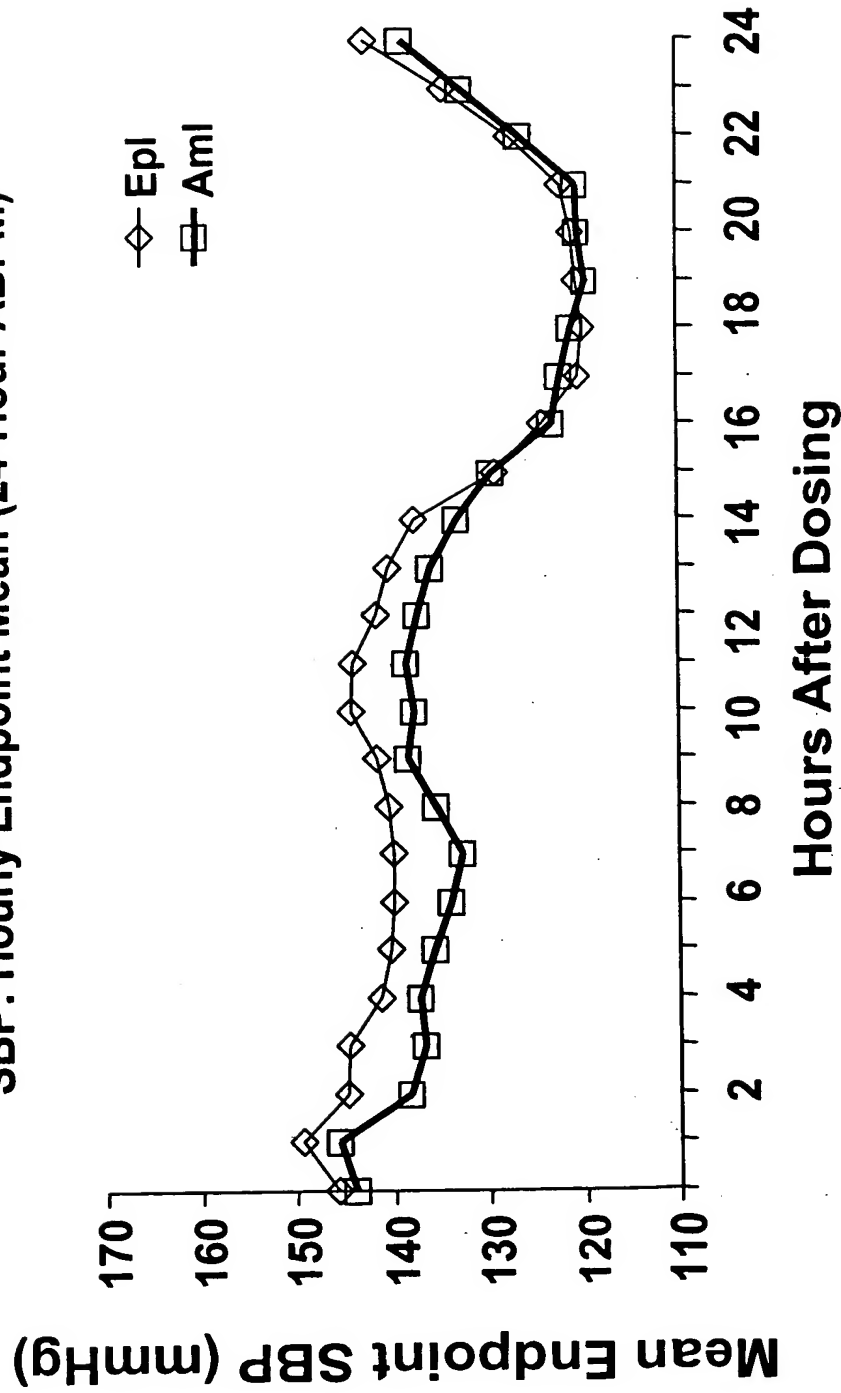
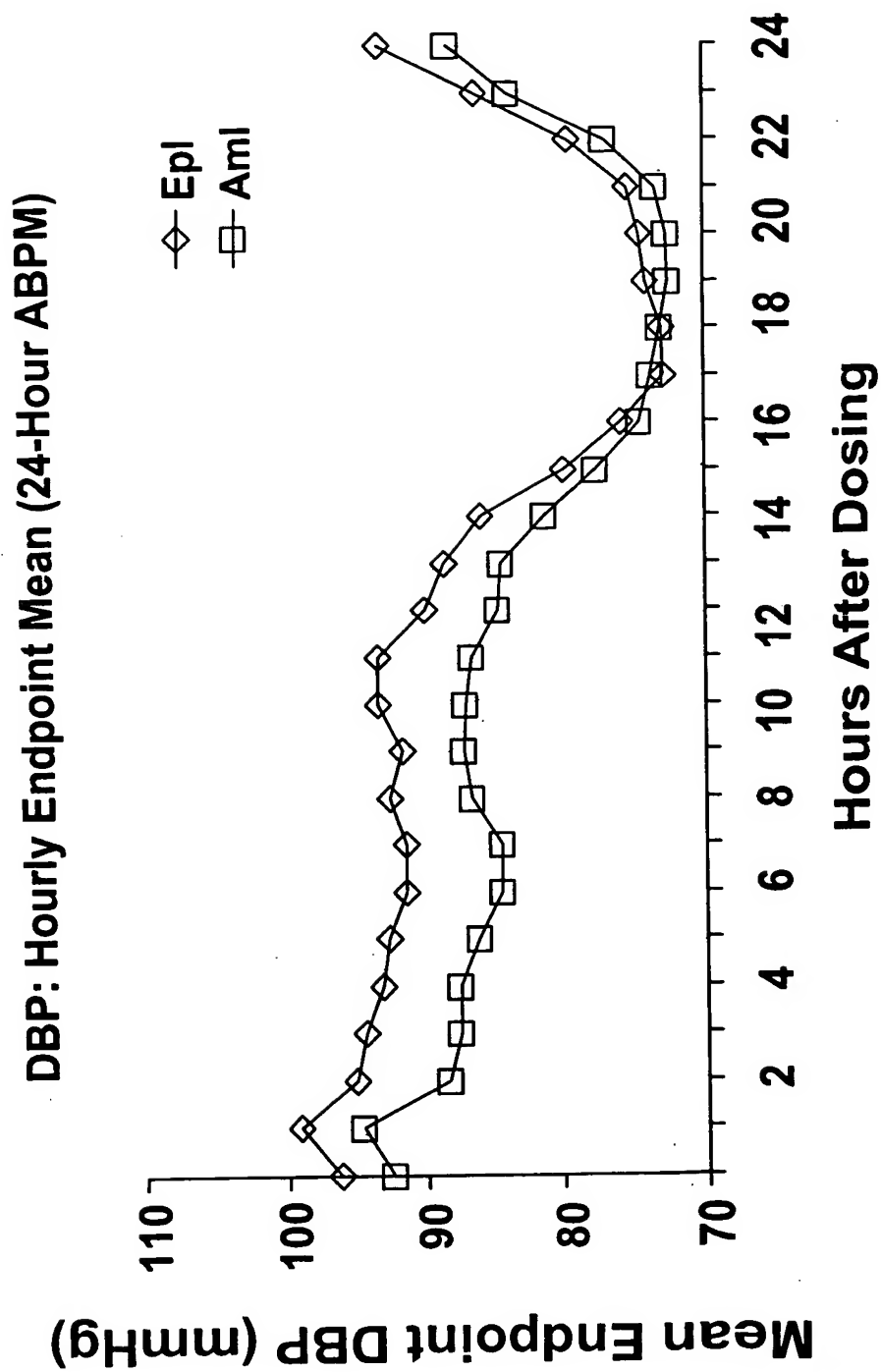




Figure D-71 - Eplerenone vs. Amlodipine in ABPM

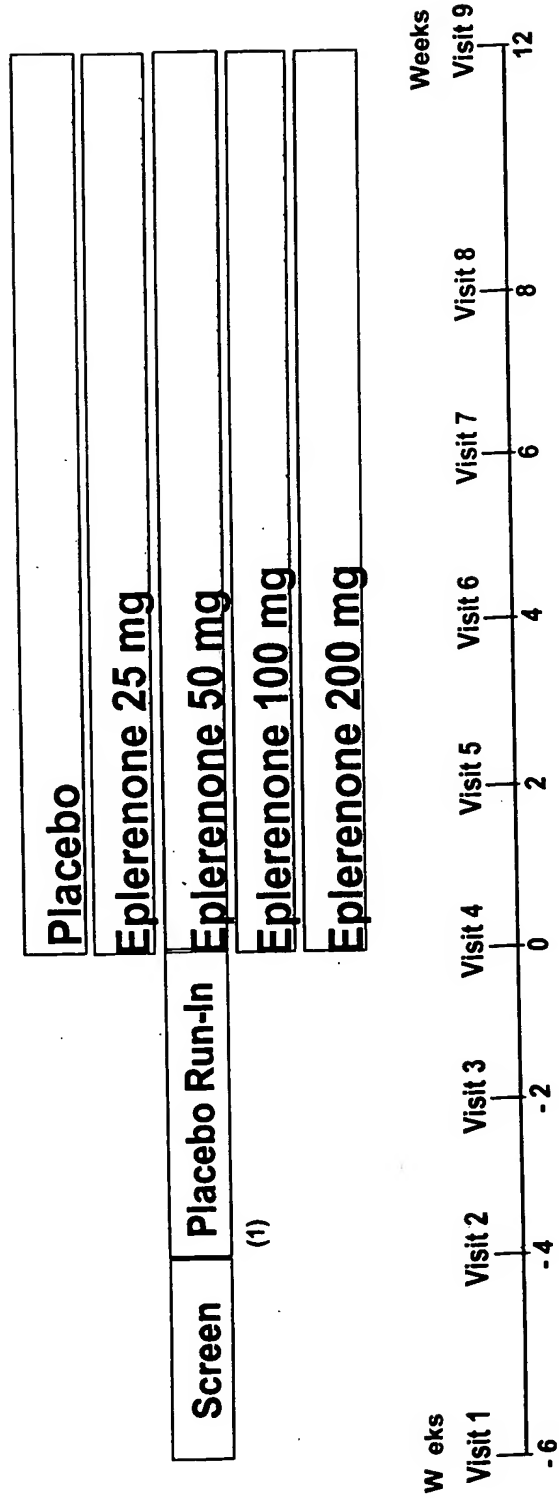


**Figure D-72 - Eplerenone vs. Amlodipine in ABPM**  
**Adverse Events of Special Interest**

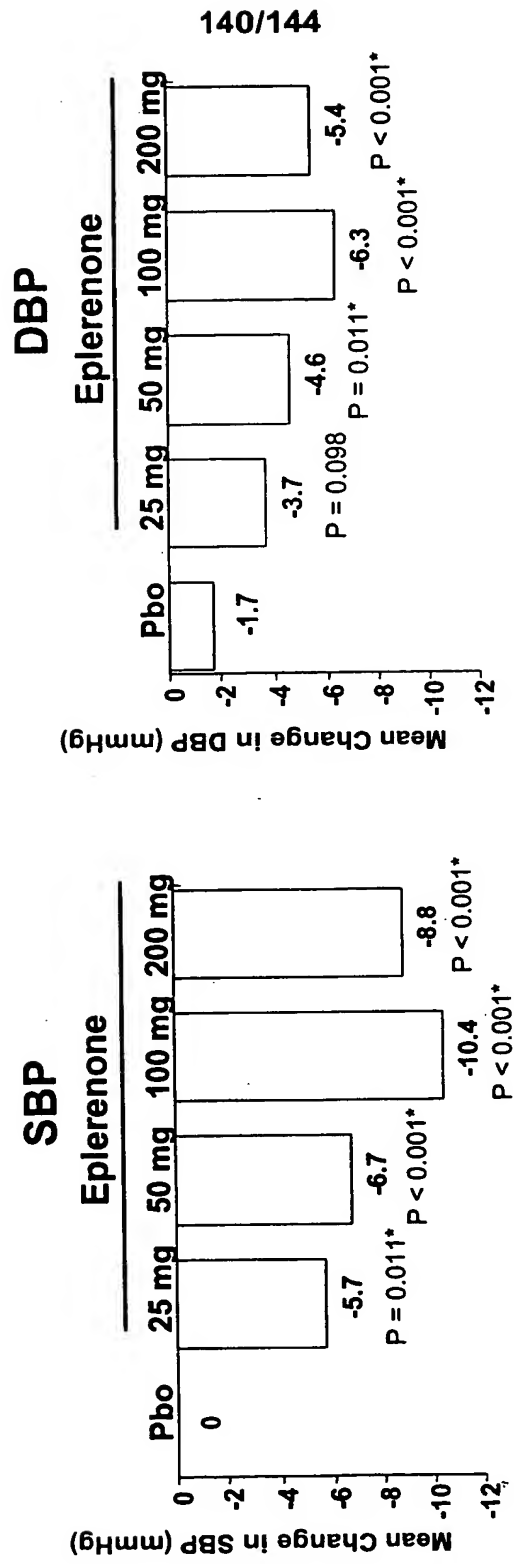
<b>AEs [N(%)]</b>	<b>Eplerenone (N=88)</b>	<b>Amlodipine (N=91)</b>
Edema Peripheral	0 (0.0)	11 (12.1)
Hyperkalemia	0 (0.0)	0 (0.0)
Hyperuricemia	0 (0.0)	0 (0.0)
Increased Lab Values		
GGT	0 (0.0)	0 (0.0)
SGOT	0 (0.0)	0 (0.0)
SGPT	0 (0.0)	0 (0.0)
BUN	0 (0.0)	0 (0.0)
Impotence*	1 (2.2)	0 (0.0)
Gynecomastia*	1 (2.2)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)
Hypokalemia	0 (0.0)	1 (1.1)
Menstrual Abnormalities**	0 (0.0)	0 (0.0)

\* N = 46 (EPL); 56 (AML)    \*\* N = 42 (Epl); 35 (Aml)

Figure D-73 - Study Schematic

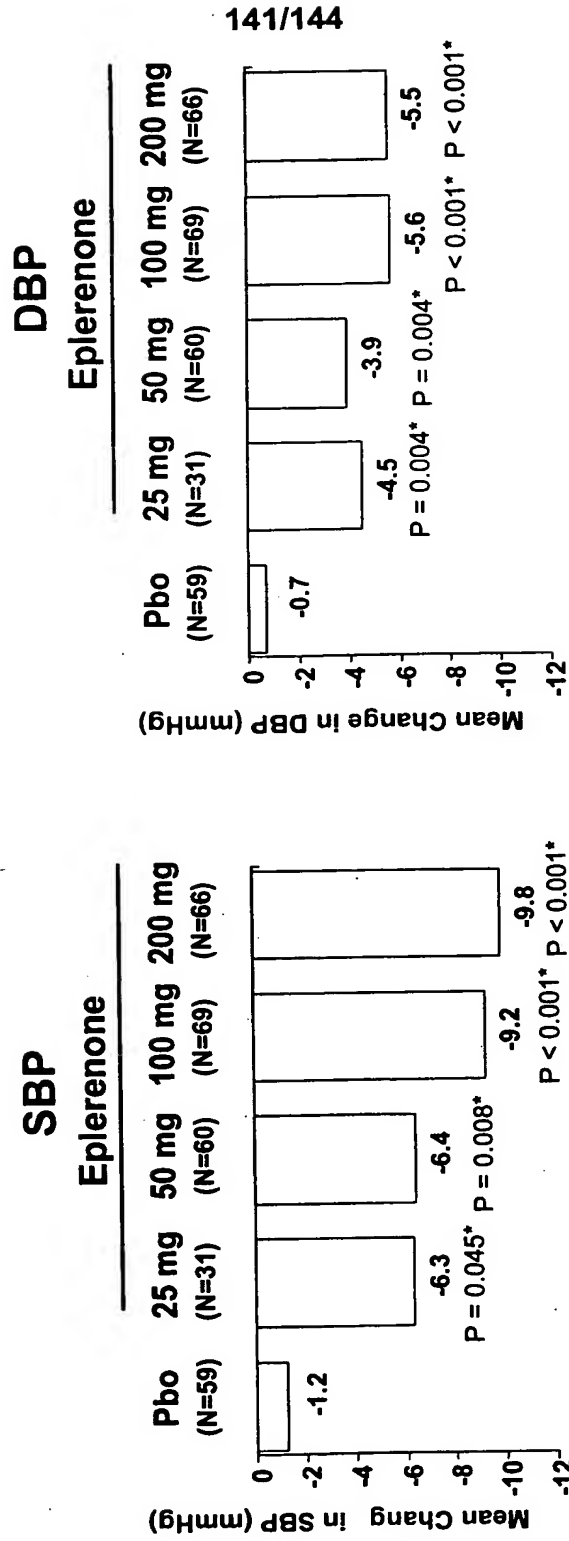


**Figure D-74 - Mean Change from Baseline:  
Cuff BP Week 12 (Final Visit)**



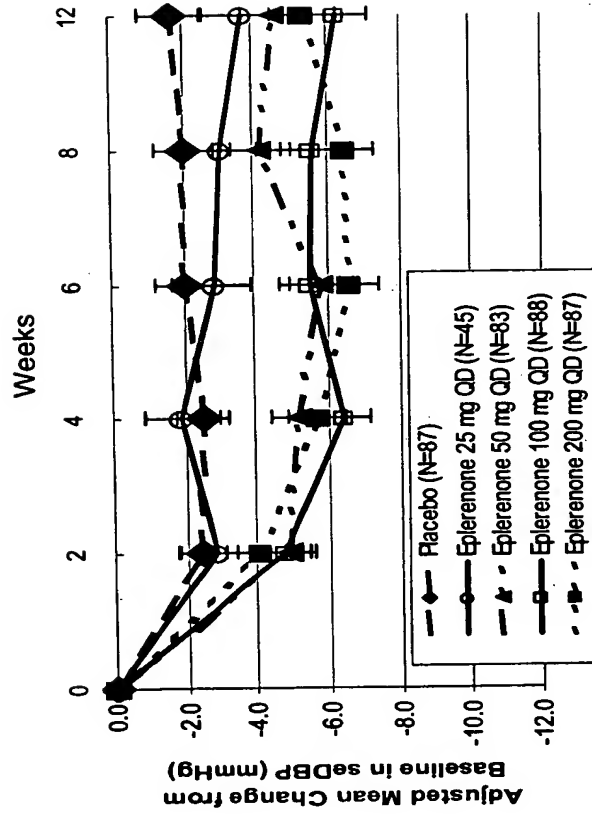
\* p-value vs. placebo based on ANCOVA using baseline as covariate and treatment and center as factors

**Figure D-75 - Mean Change From Baseline  
(ABPM)**



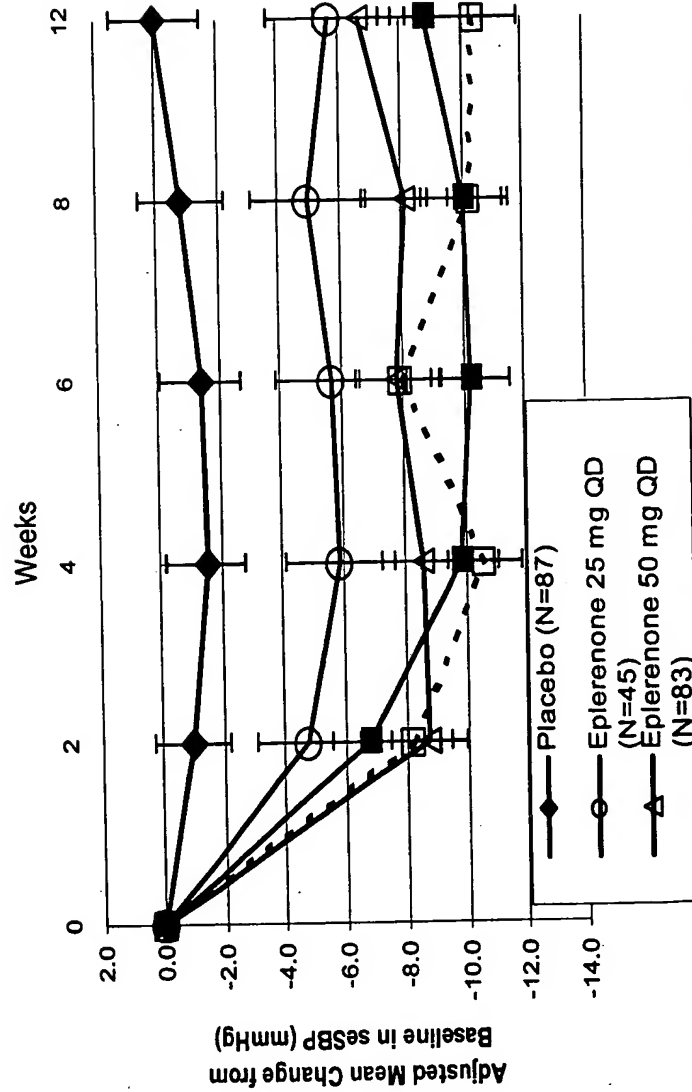
\* p-value vs. placebo based on ANCOVA using baseline as covariate and treatment and center as factors

Figure D-76: Eplerenone vs. Placebo Over Time  
Adjusted Mean Change from Baseline in Cuff seDBP



Note: Eplerenone 50 mg, 100 mg, and 200 mg QD resulted in significant ( $p \leq 0.0007$ ) reductions from Baseline in seSBP at each time point compared to placebo. Eplerenone 25 mg QD resulted in significant ( $p \leq 0.0218$ ) reductions compared to placebo at Weeks 4 and 12.

Figure D-77: Eplerenone vs. Placebo Over Time  
Adjusted Mean Change from Baseline in Cuff seSBP



Note: Eplerenone 50 mg, 100 mg, and 200 mg QD resulted in significant ( $p \leq 0.0007$ ) reductions from Baseline in seSBP at each time point compared to placebo. Eplerenone 25 mg QD resulted in significant ( $p \leq 0.0218$ ) reductions compared to placebo at Weeks 4 and 12.

Figure D-78 - Events of Special Interest

Adverse Events	Eplerenone				
	Pbo (N = 90)	25 mg (N = 45)	50 mg (N = 87)	100 mg (N = 90)	200 mg (N = 88)
Aggravated Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Hyperuricemia	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Increased Lab Values					
GGT	2 (2.2)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
SGOT	1 (1.1)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)
SGPT	1 (1.1)	0 (0.0)	1 (1.1)	2 (2.2)	0 (0.0)
BUN	1 (1.1)	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)
Impotence*	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)
Gynecomastia*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Menstrual Irregularities**	1 (2.8)	0 (0.0)	1 (2.6)	1 (2.3)	0 (0.0)

\* N=54 (Pbo); 27(25mg); 48(50mg); 47(100mg); 48(200mg)

\*\* N=36 (Pbo); 18(25mg); 39(50mg); 43(100mg); 40(200mg)